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CONTINUATION STUDY

POSTGRADUATE EDUCATION—AN EXPERIMENT

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IT SO happens that the span of my professional life coincides with the evolution, one might even say revolution, of American medical education. I have watched its developments through four decades, and have seen with wonder and admiration how it has kept pace with the compelling forces of science in every field of endeavor. When I entered the university fifty years ago, inventive genius had not yet dreamed of the automobile, moving pictures, or the airplane; the x-ray, wireless telegraphy, and the radio were yet unborn, and the phonograph was only a curiosity. Most of the inventions which are commonplace today were unknown.

The forty years of this century have witnessed greater progress in the world of science than the forty preceding centuries. As we contemplate, in retrospect, the astonishing progress in science and medicine, we marvel that the mind of man can digest it. With our amazement at the unfolding secrets of science and medicine, it is indeed gratifying to know that medical education has kept pace with it all.

The increasing dimensions of medical education are a measure of, and a tribute to, the judgment and courage of medical educators in the face of great difficulties, in correcting the weaknesses and in meeting the problems of rapidly expanding scientific knowledge. The improvements in medical education have been their answers to certain evils or needs and they can be differentiated into quite distinct phases.

NOTE: The Editors accept no responsibility for the views and statements of authors as published in their "Original Communications."

The first phase of improved medical education was the elimination of the weak, poorly equipped medical schools with which the country was afflicted forty years ago. Rapid population growth, due to unrestricted immigration and the high birth rate, created a demand for physicians, which led to a mushroom growth of nearly 400 incompetent schools—veritable "doctor factories" and "diploma mills" turning loose hundreds of incompetent so-called doctors pitifully ignorant and unskilled.

This first phase of improvement was accomplished by classification of schools by the American Medical Association, which gradually eliminated the weaker schools and raised the quality of teaching in the others.

The second phase of improvement was the elevation of educational requirements for admission to medical schools. This was brought about by educators themselves, who appreciated the fact that their students were unprepared to receive instruction in scientific medicine. An inevitable and concomitant feature of low-grade medical schools was inadequate admission requirements. To correct this deficiency high school graduation was the first added requirement for entrance into medical schools; then successively one, two, and three years of college work with certain subject requirements, and in several schools a bachelor's degree was demanded.

The third phase of improvement was the broadening of the medical undergraduate course, first, by increasing its length to four years; second, by increasing its scientific content by the addition of well-equipped and well-manned laboratories; and third, by augmenting clinical teaching with controlled hospitals under the supervision of well-trained full and part-time teachers.

The fourth phase was the improvement of the required and voluntary internships by raising their educational value through increased length of service and by better teaching. This was aided by the classification of hospitals according to the educational desirability of their internships, especially by schools which required five years to obtain the doctor's degree.

The fifth phase of improvement was the conversion of residencies from a mere long-time internship to an organized, extended training on a real graduate basis under well-trained and experienced teachers, the same as in other departments of learning.

Many medical schools have become departments of universities; hence they must conform to the standards of the graduate school and be responsible to the Dean of that school and to the President. This insures a well-educated and technically well-trained graduate student capable of, at least, beginning the practice of his specialty.

Now that better training is available and the competency of the specialist may be certified by the specialty boards, it is no longer necessary for the public to put up with the "specialist" by evolution from general practice or the six-weeks so-called training in an inferior postgraduate school, or the specialist by announcement. However, there are not enough educationally high-class residencies to supply the de-

mand of those who wish to become well-trained specialists able to pass the examinations of the specialty boards.

Hospitals connected with educational institutions are doing their part, but additional adequate residencies can only be supplied by larger hospitals which have no connection with medical schools. Many of them now offer residencies which may fall far short of the educational standards required for good graduate training; they frequently are nothing more than long internships. Their need is for higher educational standards by proper organization of a staff of specialists, teaching on a university basis, and the help of medical school teachers to raise their standards.

Here is another condition which the members of this Association can alter by insisting upon good teaching in the hospitals where they work.

Hospital staffs must realize that the intern and resident are not in the hospital just to help in operations and otherwise care for patients, but to receive an education as well. Room, board, and uniforms are not sufficient remuneration for the valuable services they render. They earn "good money" and should get it in the form of constant careful teaching in all the details of diagnosis and treatment.

When the time comes that these compensations are given, the staff members will be rewarded by better care of their patients. The reputation of the hospital will grow and it will be able to secure the best type of interns and residents, and eventually it will be accredited as a high-grade teaching hospital. When enough hospitals realize this responsibility, the needed residencies will be forthcoming and the welfare of the people will be in better hands.

Of the five phases of improvement of medical education mentioned, the first phase, the elimination of weak schools, is all but finished. The second phase, increased entrance requirements, nears solution. The third phase, the improvement of the undergraduate medical course, has developed a philosophy of education which renders its ultimate solution certain. The fourth phase, the internship, is progressing toward a satisfactory solution in teaching hospitals, but in hospitals not affiliated with teaching institutions too little has been accomplished and nothing can be expected until their staffs fully appreciate their obligation. The fifth phase, the broadened training of residents and fellows, has reached a high plane in hospitals connected or affiliated with medical schools. The weakness is in hospitals not associated with teaching institutions, where clinical experience and development of skills are not accompanied by proper teaching and training in research founded upon broad and sound pedagogic principles.

The demands for residencies and fellowships cannot be supplied by teaching hospitals. The Commission on Graduate Medical Education estimates that 50 per cent more residencies are needed for ambitious young men who desire better training for a specialty and to meet the requirements of specialty boards, which in 1942, will be increased by all boards to three full years residency or the equivalent. I fear that this need cannot be met until hospitals without teaching facilities realize that they owe an educational obligation beyond clinical experience and development of technical skill.

The real objective in the residency or fellowship is the training of a specialist over a sufficient length of time and of such a high educational quality that the finished product will redound to the credit of the hospital, insure better care of patients, and elevate the standards of medical practice.

The sixth phase in the development of medical education is postgraduate work. In the past, the term "postgraduate" bore a rather unsavory stigma because of the numerous low-grade "fly-by-night" schools which, in six weeks, produced "specialists" certified with a gloriously engraved diploma. Higher grade institutions objected to being classed with these shoddy postgraduate institutions, so they renounced the distasteful appellation and adopted the designation "graduate school." Some of the better postgraduate schools raised the quality of their teaching and became affiliated with universities.

In recent years postgraduate study has acquired a new meaning and dignity. It is now generally recognized that it is a needed development in medical education.

So important have the developments in graduate and postgraduate study become that the Advisory Board of Medical Specialties created in 1937 the Commission on Graduate Medical Education "to study the whole problem," including the internship, and graduate and postgraduate medical education.

The Commission's report, of 293 pages, emphasizes the great need for postgraduate education for the physician without too much interruption of his practice, refers to the many divergent plans for continuation study (a better term than postgraduate education), indicates their strength and weakness, and impressively insists that they must conform to highest educational standards, which, of course, is the crux of any teaching plan. In short, the report insists that, while all experiments contain something good, they all need critical analysis and some coordinating force which will secure "high standards but not standardization."

It seems rather trite to say that medicine and its allied sciences are changing so rapidly that the physician can keep abreast of progress only by continuous study after graduation. But self-improvement at home is not enough. Organized opportunities for further study, under proper educational supervision, are also necessary.

Such organized facilities first became available in a meager and halting way about two decades ago. Especially in the last ten years various and sundry courses have been offered in almost all the states. While many physicians have availed themselves of these opportunities, the response in general has been somewhat disappointing. One of the great problems of continuation study courses is to stimulate wider interest in them. The best advertising is the quality of the courses; their content to meet the needs of the physician in practice, and trained men to do the teaching.

Many experiments have been made which the Commission declares is "a desirable condition which must continue if healthy growth is to endure. Educational standards can be developed with a wide latitude

as to means." The Commission has given one point particular emphasis: continuation teaching must be separated "into two independent categories which should be clearly differentiated; namely, instruction to general practitioners and to qualified specialists."

Inasmuch as approximately 80 per cent of all pregnant women are delivered by general practitioners, it is evident that we, as obstetricians, owe an especial obligation to them to provide continuation study courses if we are to keep the general level of obstetric practice abreast of progress in our field. To accomplish this, every state within the area of this Association should have a state society of obstetrics and gynecology, however few the number of specialists may be. If there are any doubts about the feasibility of this suggestion, I refer doubters to the case of North Dakota, where there are only fifteen specialists in our field in the whole state and not one maternity hospital; yet the general profession looks to this little society for leadership in continuation study, and maternal and child welfare. Every state can do the same.

We see in this brief retrospect the improvements in medical education, that each phase was due to a challenge to the medical educators and the profession by some weakness or advancement of science, requiring change in pedagogic methods, and that the challenge has been met courageously and with sound judgment.

We have faith that the same courage and judgment will ultimately lead to a solution of the difficult problems of postgraduate study in the midst of which we are now struggling. It is encouraging to note that the meager beginnings of twenty years ago have grown to the stature of a movement. When the problems are thoroughly understood, and all motivating forces mutually attack them, the solution of the sixth phase, continuation study, will be on its way, just as the previous five phases were solved by conjoint effort.

The Commission, realizing the educational difficulties, states:

"Because graduate medical education is so new and has been growing so rapidly, there is no clear definition of its content and no accepted standards of its quality and length. . . . Therefore, there are several outstanding needs in this field. First, there is the need of a clear definition of postgraduate work for general practitioners and specialists. Second, to provide more opportunities for proper postgraduate education for each group. Third, to convince some physicians of the need for continued education.

"Postgraduate medical education may be applied to any type of systematic, supervised educational activity that helps the physician keep abreast of the developments in his field of practice, but not designed to qualify him to enter a new field (or specialty).

"While some courses offer material of true educational value, others have been either too superficial or too technical.

"There is real need, therefore, for the development of standards of educational content. Because of the newness of the field, standards have heretofore been impossible. But broad educational standards can and should now be developed."

It is evident that the Commission, while approving the experiments, is at the same time concerned about their educational value and about the type of teaching which, self-evidently, must come largely from the medical schools.

May I quote the Commission's final paragraph on postgraduate education:

"The time is now ripe for the development of broad standards of educational content of postgraduate work, standards that will emphasize objectives and stimulate higher achievement without inhibiting widespread experimentation with means and methods.

"Perhaps the most difficult problem is to recruit and train teachers who will be able to hold the attention of practicing physicians. Teachers must learn to present their subject matter in a form that is condensed and so organized that it closely integrates the applicable basic science material with practical diagnostic and therapeutic techniques. To make postgraduate study effective and of good educational content, it should be considered a continuation of undergraduate and graduate medical education."

It is obvious that this last phase of improvement of medical education is not a "thing apart" but "part and parcel" of that great movement to keep medical education abreast of scientific progress, which began just before the turn of the century, gaining momentum with each decade, actuated by the philosophy of "broad standards of educational values." We must now apply the same principles to postgraduate education, continuation study.

The heterogeneous mass of differing plans and methods must be crystallized into a sound educational philosophy. The elements are already in the mass, and the water of crystallization will be supplied by medical educators, the profession, and all organizations interested in the solution. I have no disposition to worry you with an attempt to analyze the various types of courses given to further continuation study. They are good but they may be made better. You are all familiar with refresher courses, long or short, given at or near the physician's home; courses given at medical centers; intensive courses by general and special medical societies; circuit courses by traveling teachers and consultants; courses given annually by state societies, clinical congresses, regional postgraduate assemblies, and the courses on specific subjects like the ones sponsored by the Maternal and Child Welfare Committee.

They all have their good features and their drawbacks. It may be said in general that the short courses given at or near the physician's home have the advantage of reaching more doctors, but the disadvantage that the exigencies of an active practice prevent many from attending the daily sessions. On the other hand, courses given at a medical school center have the advantages of greater educational value by virtue of a larger number of trained teachers, more hospital clinical material for demonstrations, laboratory facilities, and proximity to a large library, with nothing at all to interfere with the courses.

The Commission has cited the University of Minnesota as an example of advantageous postgraduate teaching in a center. The University has taken the matter of adult education very seriously. On its campus is a large building, The Center for Continuation Study, the brain child of a great educator, the late President Lotus D. Coffman, erected to carry out his idea of the state-wide campus or a "University for all the people."

The building is designed to offer a place for continuation study in any department of the University. It contains lecture, study, and seminar rooms, a chapel (used also for lectures), library, lounge, dining room, hotel rooms with bath, where any one attending courses may live alone or with his wife. There is a large basement garage where one may park his car at a small fee during his entire period of continuation study. In short, it offers all the facilities of a fine club in the scholastic environment of a great university. The earnest attitude of the Medical School toward continuation study is attested by the fact that, in 1936, it established a department continuation study under the direction of a full-time director, Dr. William A. O'Brien.

In addition to knowledge attained from a large, high-class faculty, there is the advantage of constant, informal discussion with other practitioners enrolled in the courses. Instead of a few hours of instruction at home, which is subject to interruption by professional calls at all times, courses at the Center afford little interference.

The courses vary from twenty-one hours for three days to thirty-six hours for six days. In the three-day courses the evenings are occupied by teaching. In the six-day courses the evenings are free. The cost of the courses is $2.75 a day for room and meals, and the tuition is $15.00 for three days and $25.00 for six days. There are no extra expenses. A unique feature in the Minnesota plan is that the courses in obstetrics and pediatrics, which are usually given conjointly, cost the out-of-town physician nothing. Expenses are paid by the Minnesota Department of Public Health from funds received by provisions of the Social Security Act. Any Minnesota county medical society may select one (occasionally more) of its members to attend the courses. The physician advances the costs and the Department of Health reimburses him. It is understood that he shall give a report of proceedings to his society, which is made easy for him by a complete mimeographed, bound copy of all lectures. These men attend, not for their own benefit alone, but they are also emissaries from their societies and return as missionaries of up-to-date obstetrics, gynecology, and pediatrics. Therefore, the benefit is state-wide and more, because county societies of North and South Dakota, under the identical plan, send representatives to the Center.

In 1939 to 1940, 129 physicians from Minnesota availed themselves of these opportunities; 72 enrolled from North Dakota and 30 from South Dakota. When we reflect that these 221 physicians from three states taking the courses in one year represent a society membership close to 3,000 physicians, the educational influence of this one Center of continuation study is indeed extensive.

However, we do not offer the Minnesota plan as a solution of the problems of continuation study. We are very critical and all who cooperate in the project still consider it an experiment. But I should like to add that whatever has been accomplished was possible only through the heartiest cooperation of all the agencies interested in continuation study: the Minnesota State Medical Association, the Minnesota Society of Obstetrics and Gynecology, the University of Minnesota Medical School, and the Minnesota Department of Public Health.

We have observed how the discoveries of science during the last half century, greater than during all the preceding centuries, have forced medical education to change through six rather definite phases.

Medical educators have developed a philosophy and methods which approach, more and more, a solution of the first five phases. We may fairly assume that problems of the sixth phase, postgraduate education, may be elucidated by the same sound pedagogic philosophy. However, solutions will not be made by "rule of thumb." Much experimentation must be undertaken.

Many plans have been proposed with some good in all of them, but with drawbacks in most of them. Their very number is at once their strength and their weakness. The numerous plans are an evidence of strength evincing a widespread interest. Their weakness lies in the fact that some of them are pedagogically unsound.

Self-evidently the problem is to find the strength and to eliminate the weakness. For these reasons, there should be wide discussion, especially by the special obstetric and gynecologic societies like this one. Medical schools inevitably should lead; perhaps by the organization of departments of postgraduate education with a full-time director. Mutual efforts by all agencies, medical schools and societies, and departments of health are the key and the final goal for the solution. While all plausible ideas should be tried, they must be critically analyzed in order that they may be proved educationally sound.

Postgraduate education should be developed so completely that it may be made available to the whole profession. To this end I suggest that this society, in order that it may do its full part, organize a symposium in which all the apparently sound methods may be presented by their supporters and discussed by all, with the hope that the soundest plans may be determined.

INHIBITION OF LACTATION*

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STILBESTROL, testosterone, and theelin have been reputed to be inhibitors of human breast secretion. For the most part, the reports assumed that breast engorgement was synonymous with breast secretion. During a study of normal lactation among 900 consecutive nursing mothers, we observed that the degree of early breast engorgement does not consistently indicate the amount of subsequent milk production. Frequently mothers with conspicuous breast distention and discomfort fail to secrete sufficient breast milk and must rely upon complementary feedings within a few days. In distinct contrast, a mother who passes through the engorgement stage in relative comfort may secrete sufficient milk for full-breast nursing. These observations have stimulated critical analysis of inhibition of lactation. We were interested in determining whether inhibition of breast engorgement is synonymous with inhibition of lactation. Other questions that arise are: What is the effect on breast secretion when stilbestrol, testosterone, or theelin is administered early in the post-partum period? If these hormones inhibit breast secretion, is the effect temporary or permanent? Will these hormones inhibit breast secretion after lactation is established and is the effect temporary or permanent?

METHOD

All babies in this study nursed alternate breasts every four hours beginning twelve hours after delivery. Water was administered during the first forty-eight hours as necessary; thereafter, complementary formula feedings were used as indicated. The babies were weighed before and after each nursing, and the total daily milk secretion was carefully recorded. All mothers were classified on the fifth and tenth post-partum days on the basis of a total twenty-four-hour milk secretion and assigned to one of three groups: full-breast, part-time, or deficient nursing. (The method of classification has been previously reported in detail.[1]) If the milk secretion was insufficient for full-breast nursing on the fifth post-partum day, the breast was emptied with an electric breast pump after each nursing. Pumping the residual milk is necessary to determine whether the baby is completely emptying the breasts at each nursing, for cases of apparent deficiency oftentimes are secreting sufficient milk to be classed as part time or full-breast nursing.

All patients receiving stilbestrol, theelin, or testosterone early in the post-partum period were carefully selected on the basis of their previous nursing record. Only mothers with good or poor records were used. Our standards of a good nursing history were based on a study of the records of 900 nursing mothers. In

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attempting to predict the present expected nursing course of any mother on the basis of her previous nursing record, we found that our highest percentage of correct predictions was among mothers with the so-called good nursing background. Only mothers who meet the three following conditions can be considered to have a good nursing history and can be expected to feed the baby entirely from breast during the present confinement: (1) the last baby was nursed entirely from breast for a period of at least two months; (2) the age of the patient is less than 35 years; (3) the date of the last confinement does not exceed three years. Predictions of the present nursing course among mothers with a poor nursing record are less reliable. We selected for this group only those with a history of the baby having been removed from breast early in the post partum because of insufficient milk secretion.

Stilbestrol was administered orally to 29 nursing mothers beginning the first post-partum day. There were 23 mothers with good and 6 mothers with poor nursing histories. Since we were interested in establishing a deficiency of lactation by the fifth post-partum day, the total dose of stilbestrol given and the number of days over which it was given varied greatly from case to case. The lowest daily dose was 5 mg., the highest was 15 mg. The total dose ranged from 10 mg. over a two-day period as a minimum to 50 mg. over a four-day period as a maximum.

The nursing background was not considered in the selection of the 23 mothers who received stilbestrol beginning the sixth post-partum day. Primiparas as well as multiparas were used, the only requirement being that these mothers were secreting sufficient breast milk on the fifth post-partum day for full-breast nursing. The daily dose varied from 5 mg. to 20 mg. The minimum total dose was 10 mg. during a two-day period, while the maximum was 60 mg. over a four-day period.

There were 15 patients who received testosterone early in the puerperium. The dose in all cases was uniform. Beginning at 9:00 P.M. on the first post-partum day, 25 mg. of testosterone were given intramuscularly. At 9:00 A.M. and 9:00 P.M. on the second and third days, 25 mg. were administered for a total dose of 125 mg.

Ten mothers nursing their babies full breast on the fifth day were given testosterone beginning at 9:00 A.M. on the sixth day. The injections were repeated every twelve hours until a total of 125 mg. had been administered.

Five mothers received injections of theelin beginning at 9:00 P.M. the first post-partum day. Each dose contained 50,000 international units and was given at twelve-hour intervals for a total of 250,000 units.

Five mothers nursing their babies full breast on the fifth day received 50,000 international units of theelin at 9:00 A.M. on the sixth day. Doses were administered every twelve hours until a total of 250,000 units had been given.

DATA

Stilbestrol, early post partum.—Six mothers with good nursing histories, who received 15 mg. to 35 mg. of stilbestrol early, secreted sufficient breast milk on the fifth and twelfth days for full-breast nursing. All of them showed some fullness of the breasts as milk secretion increased, but they were free of conspicuous breast engorgement characterized by distention and discomfort.

Six mothers with good nursing histories, who received 15 mg. to 50 mg. of stilbestrol early, were limited to part-time breast nursing by the fifth post-partum day. All six increased to full-time nursing by the tenth day. The breasts were quite soft during the first five days and showed only slight fullness as milk production increased. Breast distention and discomfort were absent throughout the ten-day period.

Among 23 mothers with good nursing histories, we were able to establish a deficiency of lactation on the fifth day in only 11. It is interesting that 8 of these 11 were nursing their babies full-breast on discharge from the hospital the tenth post-partum day. Two patients increased from a deficiency of lactation to part-time nursing, while one baby was taken off breast at the request of the mother

TABLE I. SUMMARY OF PATIENTS ADMINISTERED STILBESTROL EARLY IN POST-PARTUM PERIOD

CASE	NURSING HISTORY	POST-PARTUM DAYS STILBESTROL GIVEN	TOTAL DOSE MG.	TYPE OF NURSING	
				5TH DAY	10TH DAY
8	Good	1st through 5th	35	Full	Full breast
10	Good	1st through 5th	30	Full	Full breast
24	Good	1st through 3rd	30	Full	Full breast
9	Good	1st through 4th	30	Full	Full breast
28	Good	1st through 5th	25	Full	Full breast
2	Good	1st through 3rd	15	Full	Full breast
15	Good	1st through 4th	50	Part time	Full breast
16	Good	1st through 3rd	30	Part time	Full breast
19	Good	1st through 3rd	30	Part time	Full breast
29	Good	1st through 3rd	30	Part time	Full breast
4	Good	1st through 3rd	15	Part time	Full breast
5	Good	1st through 3rd	15	Part time	Full breast
25	Good	1st through 4th	40	Deficient	Full breast
27	Good	1st through 4th	35	Deficient	Full breast
12	Good	1st through 3rd	30	Deficient	Full breast
20	Good	1st through 3rd	30	Deficient	Full breast
22	Good	1st through 3rd	30	Deficient	Full breast
23	Good	1st through 3rd	30	Deficient	Full breast
7	Good	1st through 4th	25	Deficient	Full breast
11	Good	1st and 2nd	20	Deficient	Full breast
6	Good	1st through 3rd	15	Deficient	Part time
14	Good	1st through 3rd	30	Deficient	Part time
18	Good	1st through 4th	40	Deficient	Off breast
21	Poor	1st through 3rd	30	Deficient	Deficient
17	Poor	1st through 4th	25	Deficient	Part time
1	Poor	1st through 3rd	15	Deficient	Deficient
3	Poor	1st through 3rd	15	Deficient	Deficient
13	Poor	1st through 3rd	15	Deficient	Deficient
26	Poor	1st and 2nd	10	Deficient	Deficient

TABLE II. PATIENTS ADMINISTERED STILBESTROL AFTER THE FIFTH POST-PARTUM DAY

(All Patients Full-Breast Nursing on the Fifth Day)

CASE	TOTAL DOSE ADMINISTERED MG.	NURSING 10TH DAY	DROP IN MILK SECRETION BY 10TH DAY
1	10	Full breast	0
2	10	Full breast	0
3	20	Full breast	0
4	20	Full breast	0
5	20	Part time	55 c.c.
6	35	Full breast	0
7	20	Full breast	0
8	20	Part time	160 c.c.
9	30	Full breast	5 c.c.
10	30	Full breast	0
11	30	Full breast	0
12	40	Full breast	0
13	45	Full breast	5 c.c.
14	40	Full breast	100 c.c.
15	40	Full breast	0
16	40	Part time	105 c.c.
17	60	Full breast	50 c.c.
18	60	Full breast	50 c.c.
19	50	Full breast	120 c.c.
20	50	Full breast	100 c.c.
21	50	Full breast	0
22	50	Full breast	0
23	60	Full breast	0

on the eighth post-partum day. In all of these mothers the breasts on the fifth day were soft, and breast engorgement was not encountered during the subsequent five days in the hospital.

Six mothers with poor nursing histories, who received 10 mg. to 30 mg. of stilbestrol early, remained deficient on the fifth day, and only one of them increased to part-time nursing on the tenth day.

Stilbestrol, After Fifth Post-Partum Day.—As tabulated in Table II only 3 of the 23 mothers nursing their babies full breast on the fifth day were reduced to part-time nursing by the tenth day. In no case were we able to inhibit lactation to a state of deficiency. It is true that 10 of 23 mothers showed less milk secretion on the tenth post-partum day as compared with the fifth post-partum day, but the fall in milk production in 7 of these mothers was not sufficient to interfere with continuation of full-breast nursing. We noted no constant relation between the amount of stilbestrol given and the decline in milk secretion.

Relatively larger doses of stilbestrol were given in this part of the study. Once lactation is established, the effect of stilbestrol is much less than when it is administered before lactation is established.

TABLE III

TESTOSTERONE ADMINISTERED EARLY POST PARTUM	
Nursing on Fifth Post-Partum Day	
Full-breast nursing	13 cases
Part-time nursing	2 cases
Deficient nursing	No cases
Nursing on Tenth Post-Partum Day	
Full-breast nursing	14 cases
Part-time nursing	1 case
Deficient nursing	No cases
TESTOSTERONE ADMINISTERED AFTER FIFTH POST-PARTUM DAY	
(All Patients Full-Breast Nursing on Fifth Day)	
Nursing on Tenth Post-Partum Day	
Full-breast nursing	10 cases
Part-time nursing	No cases
Deficient nursing	No cases

Testosterone.—Table III shows that 13 of 15 mothers, each receiving 125 mg. of testosterone early in the post-partum period, were nursing their babies full breast by the fifth day. Two were part-time nursing. A deficiency of lactation was not established with 125 mg. of testosterone.

TABLE IV

THEELIN ADMINISTERED EARLY POST PARTUM	
Nursing on Fifth Post-Partum Day	
Full-breast nursing	5 cases
Part-time nursing	No cases
Deficient nursing	No cases
Nursing on Tenth Post-Partum Day	
Full-breast nursing	5 cases
Part-time nursing	No cases
Deficient nursing	No cases
THEELIN ADMINISTERED AFTER FIFTH POST-PARTUM DAY	
(All Patients Full-Breast Nursing on Fifth Day)	
Nursing on Tenth Post-Partum Day	
Full-breast nursing	5 cases
Part-time nursing	No cases
Deficient nursing	No cases

In comparison with mothers receiving stilbestrol early, breast distention and fullness were greater in the testosterone group. No mother complained of discomfort, and conspicuous breast engorgement was absent.

On the tenth day 14 mothers were secreting sufficient milk for full-breast nursing, one of whom nursing part time on the fifth day increased to full-time nursing.

Ten mothers who received 125 mg. of testosterone after the fifth day were nursing their babies completely from the breast by the tenth day. Only 2 mothers showed less milk secretion on the tenth day as compared with the fifth day. In the first and tenth patients (Cases 1 and 10) the milk decline was 145 c.c. and 65 c.c., respectively.

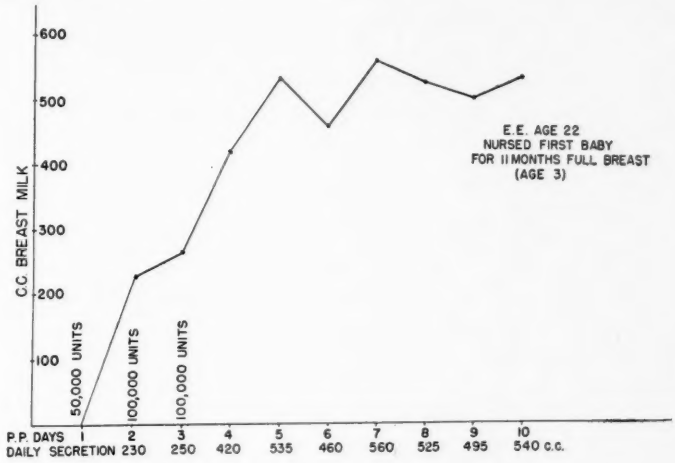

Chart 1.

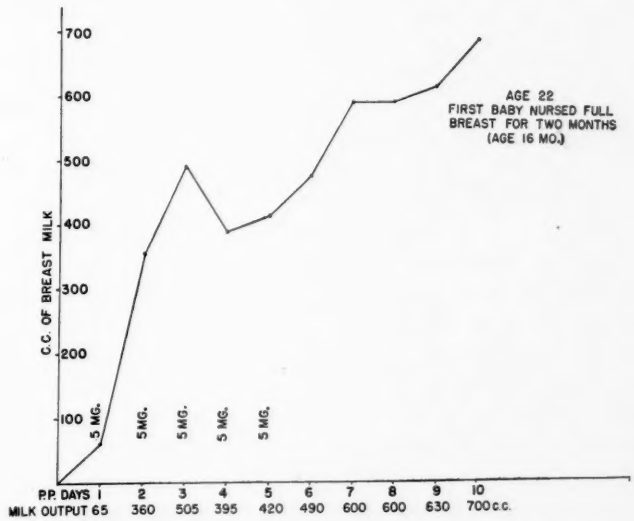

Chart 2.

Theelin.—In the small series of 10 patients receiving theelin, 5 were in the early post-partum and 5 in the late post-partum period. Each received 250,000 international units of theelin. The incidence of full-breast nursing was not affected whether theelin was administered early or late in the post-partum period. As in the testosterone series, the breasts were full but engorgement was not encountered.

Illustrated graphically in Chart 1 is a curve of daily milk secretion which is typical of the group receiving theelin early post partum. As shown by this curve, most of the mothers had a slight inhibition of lactation either on the second or the third post-partum day. This "plateau effect" is the only difference in the theelin patients as compared with those receiving testosterone. The lactation curves of those receiving theelin or testosterone after the fifth day are similar.

DISCUSSION

From the data presented in Table I, we note that patients with a good nursing background, receiving stilbestrol early in the lactation period, vary from a deficiency to full-breast nursing by the fifth post-partum day. On account of individual variation in the response to the drug, one cannot predict whether stilbestrol will cause a temporary inhibition of lactation. A dose of 15 mg. for one patient (Case 6) was sufficient to

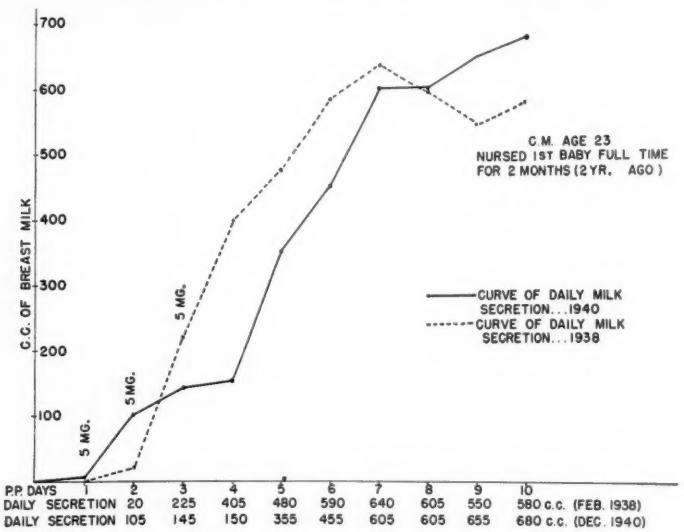
700
600
500
400
300
200
100
C.C. OF BREAST MILK
5 MG.
5 MG.
5 MG.
C.M. AGE 23
NURSED 1ST BABY FULL TIME
FOR 2 MONTHS (2 YR. AGO)
CURVE OF DAILY MILK SECRETION...1940
CURVE OF DAILY MILK SECRETION...1938
P.P. DAYS 1 2 3 4 5 6 7 8 9 10
DAILY SECRETION 20 225 405 480 590 640 605 550 580 c.c. (FEB. 1938)
DAILY SECRETION 105 145 150 355 455 605 605 655 680 c.c. (DEC. 1940)

Chart 3.

establish a deficiency of lactation by the fifth day, while another patient (Case 8) who received 35 mg. was nursing her baby full breast on the fifth day. Individual response to the drug is important in determining the degree of milk suppression.

Breast engorgement was absent in all cases regardless of the variable individual response in milk production when stilbestrol was administered early. Breast fullness was more noticeable in mothers nursing their babies full breast on the fifth day than in mothers with part-time or deficient nursing, yet none had manifest breast engorgement so vividly remembered from previous pregnancies. These observations signify that absence of breast engorgement is not a good indicator of subsequent milk production and that inhibition of engorgement is not synonymous with inhibition of lactation.

Chart 2 presents a typical lactation curve for the 6 mothers receiving stilbestrol early post-partum with sufficient breast milk for full-breast nursing on the fifth post-partum day. The amount of the drug and the dates of administration are

shown. There is a rapid rise in milk secretion the first three days. A definite fall the fourth day is in contrast with the "plateau effect" in the theelin curve of Chart 1. With the secondary rise in milk secretion after the fifth day, breast fullness increases without engorgement.

Chart 3 illustrates the type of curve obtained from the 6 mothers with part-time nursing on the fifth day. Previous nursing records serve as control for comparison. This chart shows the average daily secretion of breast milk during a previous as well as a recent admission. Stilbestrol delays the rise in the lactation curve temporarily, but the effect disappears rapidly after the medication is stopped.

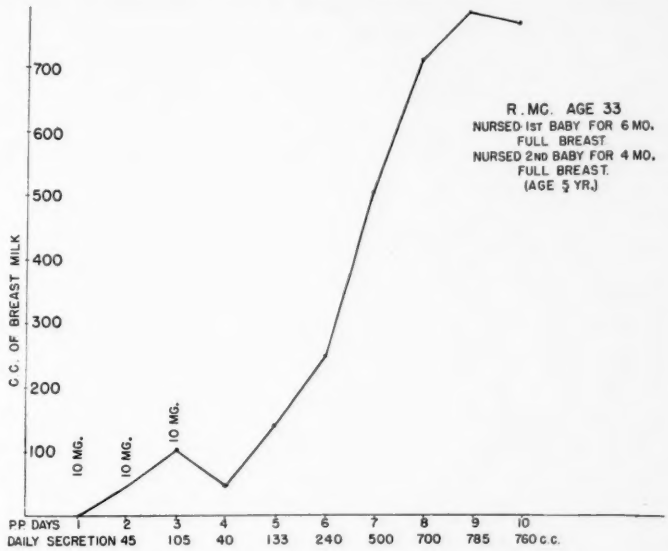

Chart 4.

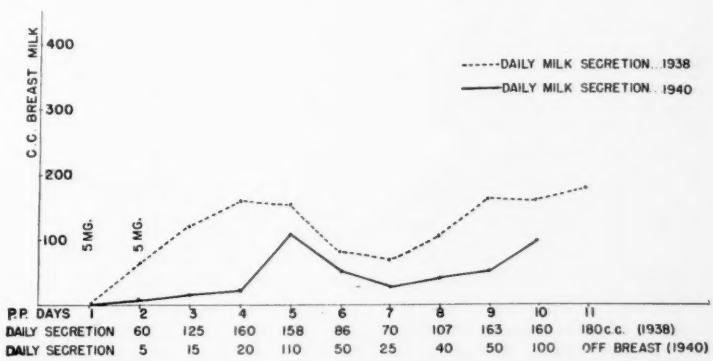
C.C. BREAST MILK
400
300
200
100
5 MG.
5 MG.
------DAILY MILK SECRETION. 1938
——DAILY MILK SECRETION. 1940
P.P. DAYS 1 2 3 4 5 6 7 8 9 10 11
DAILY SECRETION 60 125 160 158 86 70 107 163 160 180 c.c. (1938)
DAILY SECRETION 5 15 20 110 50 25 40 50 100 OFF BREAST (1940)

Chart 5.

Chart 4 shows a curve typical for the group of 8 mothers in which a deficiency of lactation was established temporarily with stilbestrol. The curve was taken from a patient who presented an excellent nursing background. The absence of engorgement on the third day alarmed her because she feared this was an indication of permanent insufficiency of milk to feed the baby. She was soon reassured by the characteristic rise in milk after the drug was discontinued. Most mothers showed no increase in milk secretion for forty-eight hours after the stilbestrol was discontinued (third to fifth days). The patients who will be discharged with full-breast nursing can be predicted on the basis of the sixth and seventh day

output. If the milk secretion on the sixth day is approximately twice that of the fifth, and the seventh day is twice that of the sixth, full-breast nursing may be predicted with confidence. All deficiency cases discharged on the tenth day with full-breast nursing show this characteristic rise after the stilbestrol has been discontinued for forty-eight hours.

The temporary deficiency due to depression of secretion by stilbestrol may be contrasted with true deficiency in the control. Among 900 consecutive nursing mothers none of those with deficient lactation on the fifth day were discharged with full-breast nursing on the tenth day.

Chart 5 shows a deficiency curve characteristic for 6 mothers with a poor nursing background. A deficiency curve obtained from the same patient in 1938 (without stilbestrol) is presented for comparison. On the basis of a comparative study of lactation curves in the deficiency group, we found that stilbestrol will further inhibit, but not completely suppress, lactation. Patients with poor or

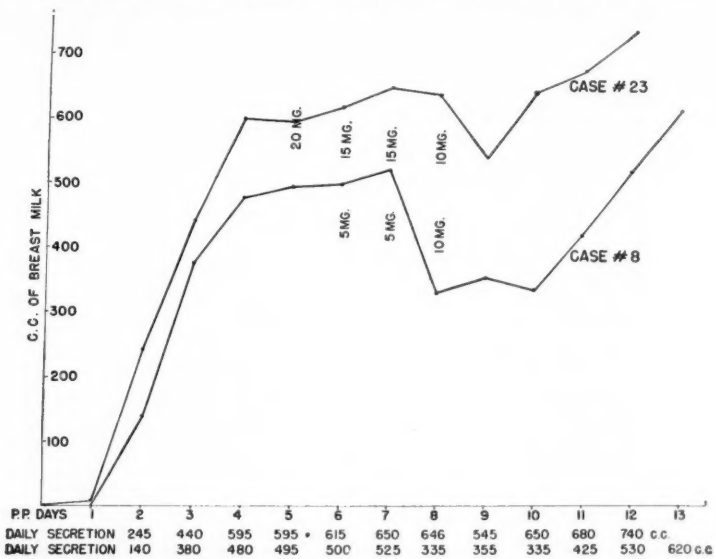

Chart 6.

deficient nursing records are not suitable for a study of inhibition of lactation. While all those receiving stilbestrol will show absence of breast engorgement, deficiency of lactation on the fifth day, and absence of rise to full-breast nursing by the tenth day, many patients will show the same without the administration of stilbestrol.

When stilbestrol was administered after the fifth day to full-breast nursing mothers, it was not possible to reduce milk secretion to a deficiency level in any case. It was not possible to decrease milk secretion in all cases. The amount of decline was not proportional to the dose administered.

The curve of Case 8 is presented in Chart 6 to show the most marked drop in this series. The temporary effect lasting for forty-eight hours was followed by a rapid secondary rise. In the same chart is the curve of Case 23. This mother received three times the dose of stilbestrol given to Case 8, but presented only a minor change in the curve of secretion. A comparison of these two curves serves to illustrate our observation that the lower the curve of full-breast secretion, the less is the dose of stilbestrol required to depress the lactation curve. The amount of diminished secretion varies greatly with the individual case.

It is our opinion that testosterone and theelin inhibit breast engorgement. When either of these substances is administered early or

late in the post-partum period, the effect on the milk secretion is negligible. There is a slight alteration in the rise of milk secretion when theelin is given early, while no effect is noted with testosterone. This is illustrated in Chart 1.

We found it necessary to discontinue stilbestrol in 2 patients because of nausea. In no case did vomiting follow the administration of this drug. The lochia remained normal in all patients during the hospitalization period. Three persons of the stilbestrol and 2 of the testosterone series reported that the lochial flow increased within a few days after discharge from the hospital.

CONCLUSIONS

Inhibition of breast engorgement is not synonymous with inhibition of lactation.

Engorgement of breasts may be prevented by suitable doses of stilbestrol, theelin, or testosterone.

Lactation may be diminished temporarily by stilbestrol, but the individual response varies widely.

The effect of 250,000 international units of theelin and 125 mg. of testosterone on lactation is negligible.

We wish to express our appreciation to E. R. Squibb and Sons for their generous supply of stilbestrol; to Parke, Davis & Co. for theelin, and to the Schering Corporation for testosterone. We also wish to express our appreciation for the assistance of Miss Hitchingham and her assistants for weight records.

REFERENCE

(1) *Stewart, H. L., Jr., and Pratt, J. P.:* Effect of Prolactin on Mammary Gland Secretion, Endocrinology **25:** 347, 1939.

712 Cass Avenue.

DISCUSSION

DR. A. W. DIDDLE, Iowa City, Iowa.—Our interest at the University Hospitals has been primarily in the action of stilbestrol and testosterone propionate on breast engorgement and to a lesser degree in the effect of the former on breast secretion after lactation has been established.

Results are available on 60 mothers, ranging in age from 17 to 39 years. Fifty-four of these neither nursed their babies nor had their breasts pumped, while 6 fed their newborn on alternate breasts every four hours. Twenty-five patients were primiparas and 35 were multiparas. Ten mothers received 25 mg. of testosterone propionate every other day until a total of 75 mg. were administered, beginning on the second post-partum day. Stilbestrol was given to 50 women. Forty received the drug within the first twenty-four hours, 35 of the 40 being given 5 mg., and the other 5, 10 mg. in a single dose. Five patients received 5 or 10 mg. of stilbestrol on the second day post partum, while 4 others were given larger doses—10 mg. every day for two or three days. Another patient received two doses of 5 mg. each in one day, two months post partum for inhibition of lactation.

Observations were made for purposes of comparison on 60 post-partum women who received no treatment and who never nursed their babies. In this group breast engorgement was noted on the second to fifth post-partum day, but it usually occurred on the third day. Only 2 had no distention or tenderness of the breasts. The duration of congestion ranged from eighteen to seventy-two hours, with the average range twenty-four to thirty-six hours.

Those patients who were treated with testosterone had symptoms comparable to the untreated group. The drug had no apparent effect.

Administration of stilbestrol gave interesting results. Twelve of 23 primiparas, who received 5 mg. of stilbestrol in a single dose the first day, had no engorgement or pain in the breasts, while 8 others had some discomfort for a few hours on either the third, fourth, or fifth day. These patients, however, did not have the usual amount of engorgement associated with the period when lactation begins. Three patients showed no demonstrable effect.

Twenty of 27 multiparas receiving stilbestrol gave a satisfactory nursing background. Fourteen of these women received 5 mg. of the drug the first day post partum; 4 had mild engorgement of the breasts on either the fourth or fifth day, while the breasts of the remaining 10 remained soft. Ten milligrams of stilbestrol were given to 4 patients on the first post-partum day; 3 had some lactation but no engorgement; the fourth showed no effect. Three mothers, who had chronic engorgement of the breasts associated with pain due to excessive lactation, were given repeated doses of 10 mg. each until they received a total of 20 to 30 mg. In 3 mothers the breasts became soft, but continued to lactate; in the fourth, lactation was inhibited so that there was insufficient milk for the infant, but by stopping treatment the milk supply gradually came back to normal within three days. This effect was also observed in 2 other mothers who received a single dose.

Since only one in 50 patients had clinically a toxic reaction (nausea), it is apparent that stilbestrol produces toxic reactions in fewer post-partum patients than in nonpregnant patients. Inhibition of breast engorgement was obtained in many mothers with relatively small doses of stilbestrol provided the drug was given the first day post partum. Many of these individuals continued to lactate for several days. On the other hand, although our observations are inadequate, we are inclined to agree with Dr. Pratt that some inhibition of lactation is possible even when the mother is nursing the baby. The impression is gained that inhibition of breast engorgement is not synonymous with inhibition of lactation.

DR. HERBERT E. SCHMITZ, Chicago, Ill.—In a recent publication I gave our results of the study of involution in those patients receiving oxytocics. Certain of these patients were unwed mothers at St. Vincent's Hospital, and they received 1 mg. of stilbestrol daily for from three to six days in order to control engorgement of the breasts. It was our observation that involution was delayed in these patients. I wonder whether Dr. Pratt has made the same observation.

DR. H. CLOSE HESSELTINE, Chicago, Ill.—Dr. Pratt and Dr. Stewart have pointed out very clearly the necessity for adequate controls and have made strenuous efforts to keep the study balanced. Many factors affect lactation. It varies even in the same individual in different pregnancies but otherwise under the same circumstances. Such factors make proper controls necessary.

Dr. M. Edward Davis and his colleagues, Dr. Louis Clancy and Dr. Simon Wolters, have a similar study well under way at the present time at the Chicago Lying-in Hospital. He and Dr. Clancy have studied 140 patients in whom they attempted to relieve engorgement or to suppress lactation by giving stilbestrol 5 mg. daily for a total of 25 to 50 mg. Of this number, two-thirds were multiparas and one-third were primiparas. The great majority of them were patients at or near term. The indications for therapy were found in patients who could not nurse because of stillbirths, active pulmonary tuberculosis, inadequate lactation or nipple and breast lesions, etc.

The findings at the Lying-in Hospital agree in general with what Dr. Stewart and Dr. Pratt report. Dr. Clancy found a great variation in the degree of suppression with most patients having a distinct inhibition of lactation, but practically all had some expressable secretion at the end of ten days. Their observations indicate that it was much easier to prevent the initial engorgement of the breasts by the early administration of stilbestrol than it was to suppress lactation once lactation had been established. Dr. Wolters administered the same amount of stilbestrol preparation for five to eight days to 15 nursing multiparas. Partial and complete suppression occurred in many, but 7 had sufficient milk for the baby on the discharge date. Thus, Dr. Davis and his colleagues demonstrate complete lactational inhibition in some, while others lactate adequately under the stimulation of

nursing or immediately after the withdrawal of stilbestrol. Moreover, they made the interesting observation that puerperal patients tolerate this larger dosage better than others, for there were no instances of nausea and vomiting.

DR. KARL JOHN KARNAKY, Houston, Texas.—On our obstetric service at the Jefferson Davis Hospital in Houston, we found one baby who developed diarrhea while we were giving stilbestrol to the mother. When we took the mother off the drug, the baby returned to normal. However, this is only one case, and we have had 20 delivered patients in all to whom we gave 5.0 mg. of stilbestrol for twenty days. We found the babies were able to nurse the same as if the mothers were not receiving stilbestrol.

We have investigated the alleged toxicity of stilbestrol in great detail. We completed 2,058 laboratory tests on 426 charity patients over the course of fifteen months. We gave doses varying from 3.5 mg. up to as high as 36,000 mg. I have published an article in the September, 1940, issue of the *Texas State Medical Journal* proving that stilbestrol is not toxic. I am fortunate to be able to keep patients in the hospital as long as I desire, or until they are taking about as much stilbestrol as necessary. Still they are not sick nor do any changes take place in their blood chemistry.

One patient was receiving 254 mg. of stilbestrol when she was accidentally killed. From the autopsy I have all the tissues and these show no changes in the kidney, liver, or other organs.

I now give 25.0 to 100 mg. of stilbestrol intramuscularly to every patient who has uterine bleeding and who comes to our charity hospital.

I have at present one woman who has taken over a course of fifteen months 36,000 mg. of stilbestrol. Her initial dose was 0.1 mg. every day and this has been increased until she gets 100.0 mg. every day by mouth and 200 to 5,000 mg. intramuscularly once or twice a week. She has had a complete blood chemistry every two to three weeks.

We have treated in all more than 1,100 patients with stilbestrol. We have observed that when we give 5 mg. the first night, the patient has nausea the next morning, but if she takes another 5 mg. the next night she is 50 per cent less sick than on the first morning. The 5 mg. of the third night only gives about 25 per cent of the sick feeling of the first morning. After the fourth or fifth 5 mg. tablet, these patients are no longer ill and can take 5 mg. tablets, one every night, for twenty to sixty nights.

DR. FRED J. TAUSSIG, St. Louis, Mo.—May I just say a word about experimental methods. When we have a problem that we wish to study we should, as far as possible, try to reduce the number of variables. Furthermore, we should wait until we have a sufficiently large number of cases to justify drawing conclusions. In the third place, control experiments should, whenever possible, be employed.

For these reasons, it seems to me that if Dr. Pratt and his co-workers had limited their experiments to *one* organic compound, still retaining the variants of the previous nursing experience and the time post partum at which the medicine was employed; and if they had studied at least 100 of each of those series with two variants; and if they had also taken every other patient who came during this period of time and employed no medication whatsoever, then their conclusions would be controlled and more valuable. In judging the therapeutic result of hormonal extracts, I think we should be extremely careful to employ such controls and such larger series of experiments before coming to any conclusion.

DR. PRATT (closing).—Inasmuch as Dr. Diddle and Dr. Hesseltine agree we have no cause for argument.

Dr. Schmitz asks whether stilbestrol causes any delay in involution. We have made no day to day observations to check this relation, but the routine postpartum examinations have revealed no difference in involution between the patients who received and those who did not receive stilbestrol.

Dr. Karnaky reports the occurrence of diarrhea in a baby nursing from a mother who was receiving stilbestrol. We have experienced no similar occurrence. While we have not measured the amount of stilbestrol in mothers' milk, our experience with sulfanilamide may be cited. It is not possible to give a nursing mother

enough sulfanilamide to have her excrete a therapeutic dose of the drug in her milk. It is probable that the excretion of stilbestrol is in the same proportion.

Opinions concerning the toxicity of stilbestrol vary widely. In a large number of patients that we have studied for their reaction to stilbestrol, we have found a relatively low toxicity in pregnant as well as in nonpregnant women. In none of the pregnant women studied was it necessary to discontinue the preparations on account of toxicity. Among the nonpregnant women we noted about 4 to 8 per cent responded unfavorably. Critical analysis of all the circumstances reduces the number that appear to have toxic reactions. One woman who may have been classed as manifesting toxic symptoms had been receiving stilbestrol for several months. She left the city for six weeks, carrying a supply of the preparation with her. During her absence she developed a gall bladder attack, with nausea and vomiting and epigastric distress. She took the stilbestrol regularly when not vomiting and continued to take it until she reported later. The acute attack ran the usual course and was apparently not influenced by the medication. Had she begun to take stilbestrol coincident with the onset of the gall bladder attack, the vomiting would probably have been attributed to the medication. In contrast to this case we may cite the experience of a woman who was nauseated the first day she took stilbestrol and vomited the second day. She discontinued the drug on her own initiative. Later she was given a placebo which produced no symptoms. A second attempt to use stilbestrol gave the same result as on the first occasion. This patient should unquestionably be classed as toxic. Only about 4 per cent of our cases gave this experience. In all instances they stop the medication voluntarily. We have found no harmful effect from the use of stilbestrol.

I appreciate what Dr. Taussig said about variables and heartily agree that we must have numerous observations. If he will reflect for a moment he will realize that it takes considerable time and effort to get 900 controls. Even this number does not justify final conclusions, but it should show the trend. We feel that this number of observations justifies a report at this time and hope that others will contribute their experience with controlled experiments. Isolated cases selected at random do not furnish a satisfactory basis for drawing conclusions. Adequate controls are necessary.

BLOOD PROTHROMBIN LEVELS IN THE NEWBORN*

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(From the Department of Obstetrics, Indiana University Medical Center)

THE demonstration by Dam and Schönheyder[1] in Denmark (1934) and by Almquist and Stockstad[2] in this country of an antihemorrhagic vitamin has resulted in widespread investigations. Dam named this substance vitamin K. In 1936 Dam, Schönheyder, and Tage-Hansen,[3] and subsequently Quick,[4] demonstrated a relationship between vitamin K and the prothrombin level of the blood, and the latter suggested that man might suffer from faulty absorption of vitamin K because of the lack of bile in the intestine. Warner, Brinkhous, and Smith,[5] and immediately thereafter Butt, Snell, and Osterberg,[6] demonstrated the value of vitamin K and bile in the bleeding tendency of obstructive jaundice. Continued investigation[7-9] has verified the importance of vitamin K in the establishment and maintenance of adequate prothrombin levels in the blood.

*Prize Award Essay, Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

This study has been aided by a grant from the Landon Research Fund of the Indiana University Medical Center.

More recent investigations have concerned the prothrombin content of the blood of newborn infants.

Brinkhous, Smith, and Warner[10] reported in 1937 that the prothrombin content in the blood of newborn infants is less than 40 per cent of the adult level, and does not exceed this level during the first two weeks. It reaches the adult level at the end of the first year. In a subsequent report,[11] these workers describe a previously unrecognized additional drop in prothrombin level which occurs between the second and sixth days of life. They believe that a rapid convertibility of prothrombin partially compensates for the deficient quantity of prothrombin demonstrated by them throughout early infancy. Quick and Grossman[12] reported (1939) that normal levels were present in infants three days or older and that in babies six hours old the values ranged from 70 to 80 per cent of the adult normal. In two of three babies one day old, marked reduction of the prothrombin level was noted, but this low level was of short duration and spontaneously returned to normal in one or two days. Waddell and Guerry[13] demonstrated (1939) a marked decrease in the prothrombin level in some infants, with the greatest drop on the second and third days of life. They also demonstrated the ability of a vitamin K concentrate given orally to newborn infants in preventing this reduction. Additional reports confirming these general findings have been published during the past year by Hellman and Shettles,[14] Bray and Kelley,[15] and Kato and Poncher.[16]

Routine study of a large series of infants has been complicated by the necessity of repeated venepuncture to obtain blood for study. Recently Bray and Kelley,[15] and Kato,[17] have reported the use of capillary blood obtained by heel puncture as giving satisfactory results. During the past year we have been using a modification of the Smith[18] bedside test reported by Smith and his co-workers[18] as a simple clinical method for evaluating the prothrombin factor in the blood of the newborn infant.[19]

METHOD

Twenty cubic millimeters of a thromboplastin extract are placed on a clean glass slide. Blood is obtained by heel puncture from the infant to be tested. Twenty cubic millimeters of blood are immediately mixed with the drop of thromboplastin extract. The drop is pricked every second with a stylus until a firm fibrin strand adheres to the point. The interval in seconds is recorded as the prothrombin clotting time. A normal control reading is obtained in the same manner using adult finger blood. The prothrombin level is expressed in per cent of normal, using the formula suggested by Smith and co-workers:

$$\frac{\text{Clotting time of control}}{\text{Clotting time of unknown}} \times 100 = \text{Clotting activity in per cent of normal.}$$

The thromboplastin extract is prepared in the following manner: Fresh sheep or swine lung is ground and placed in a large beaker. To this is added 1 c.c. of normal saline per gram of ground lung. The lung-saline mixture is stored overnight in the refrigerator. It is then strained through a double layer of broadcloth. The saline extract is placed in small test tubes and stored in the freezing compartment of a refrigerator where it retains its potency for at least six weeks. When ready for use, a tube is allowed to thaw and is used at room temperature.

We wish to emphasize that an accurate determination of the prothrombin level in the blood is not obtained with this method. The ability of the blood to clot in the presence of an excess of thromboplastin is measured and in this way a summation of several factors is estimated, including, particularly, the amount and convertibility of prothrombin. We feel that such a test gives a satisfactory clinical assay and will indicate those infants in whom a critical deficiency of prothrombin exists.

RESULTS AND COMMENT

Control Infants.—A total of 182 infants have been studied. Determinations of the prothrombin clotting time were made at least every other day during the first ten days of life or for longer periods if the infant remained in the hospital. In

many instances daily readings were made from birth until the fifth day. Fig. 1 illustrates in per cent of normal clotting activity, the average level for each day of life in the total group. It will be noted that the average reading on the day of birth is 65 per cent of normal; this has varied from 40 to 100 per cent of normal. There is a drop during the early neonatal period which reaches the lowest level during the third twenty-four-hour period. This is followed by a rapid spontaneous rise, so that at the end of the first week of life the level of clotting activity is above that at birth.

There is, however, a wide variation in the curves of individual infants. This is illustrated by five graphs shown in Fig. 2. These were all normal full-term infants delivered without unusual incident. This marked variation is difficult of explanation. We find suggestive evidence that there is a seasonal variation in the type of curve. In 10 infants delivered during November, 1939, the average low reading was 45 per cent, while in 10 infants delivered during March, 1940, the average low reading was 12 per cent of normal clotting activity. Further study

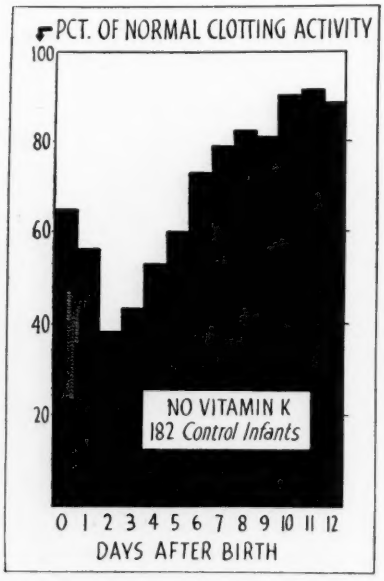

Fig. 1.—Control infants.

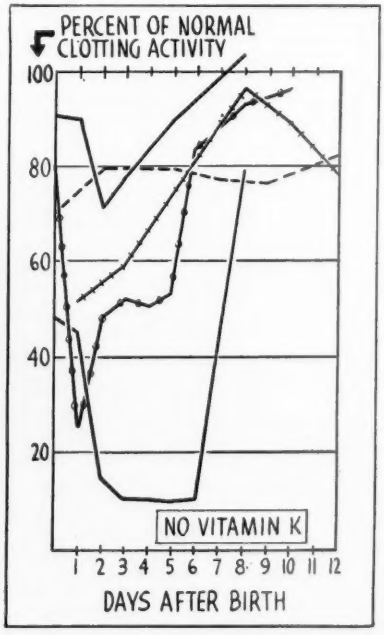

Fig. 2.—The variation in normal infants.

of this phase is being made. The observation is not surprising, however, in view of the probable difference in the diet of the average patient during the summer and winter months. We have been unable to establish any correlation between the type of curve in the infant and the level in the mother's blood. In 250 mothers tested there was none in whom a reading below 70 per cent was obtained.

In 19.7 per cent of this control group the level of clotting activity dropped below 30 per cent of normal. These marked decreases in clotting activity and the surprisingly rapid return to normal levels are illustrated in Fig. 3. Both of these infants were entirely normal as far as could be determined clinically. In several instances in this group the return to normal levels has been delayed to the seventh and eighth days without the development of untoward symptoms. One must consider such infants, however, as having a potential bleeding tendency.

During the period of the present study there have been 30 premature infants delivered. Nine of them were in the group which did not receive vitamin K. A composite curve for these infants (Fig. 4) does not indicate unusually low levels as have been reported by Hellman and Shettles,[14] but confirms the observations of Kato and Poncher.[16]

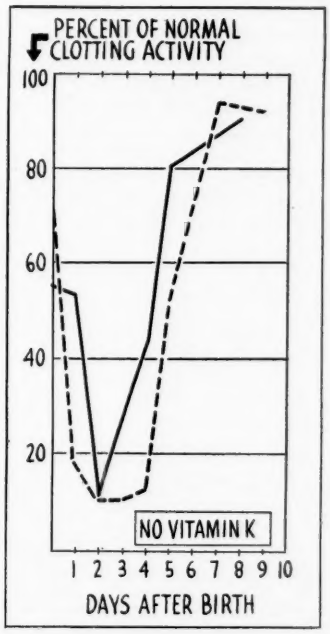

Fig. 3.

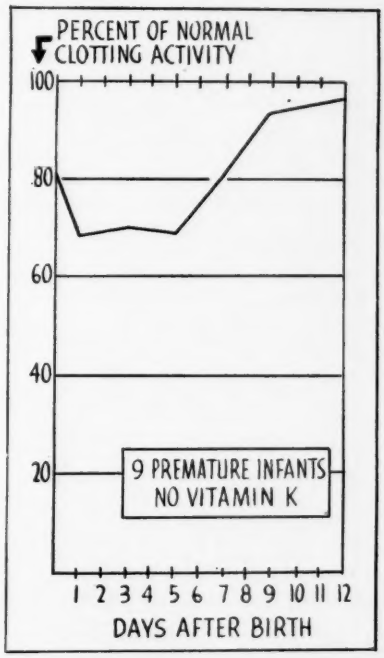

Fig. 4.

Fig. 3.—The marked drop which occurs in some normal infants.
Fig. 4.—An average curve for premature infants.

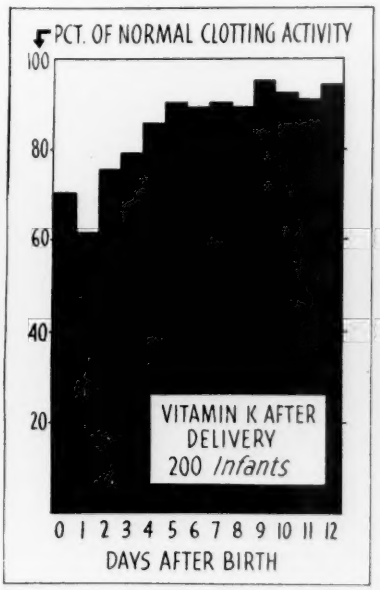

Fig. 5.

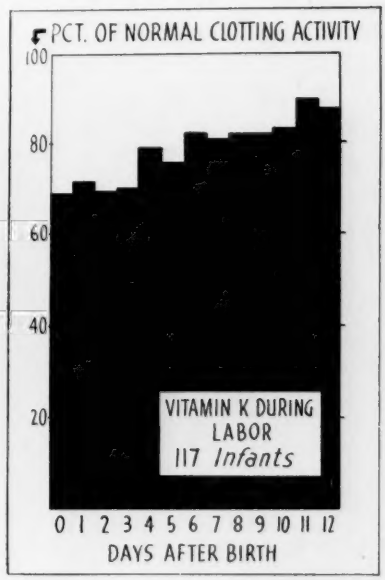

Fig. 6.

Fig. 5.—The administration of vitamin K six and thirty hours after delivery.
Fig. 6.—The administration of vitamin K during labor.

Vitamin K After Delivery.—To determine the effectiveness of vitamin K in the prevention of this observed drop in prothrombin clotting time, a vitamin K preparation (2 methyl-1, 4 naphthoquinone)[20] was given routinely to a series of 200 infants. The dosage employed was empirically chosen to be 1 mg. given orally in corn-oil solution 6 hours and 30 hours after birth. For purposes of evaluation it has not been changed. The composite curve obtained in this group of infants is illustrated in Fig. 5. It will be seen that the decrease in clotting activity, characteristic of the control group, is essentially absent, and the lowest level is 62 per cent. There is again a rise above the level recorded during the first day of life and a maintenance of that higher level. The slight drop which does occur during the second twenty-four-hour period may hypothetically be explained upon the basis of an insufficient dosage of the naphthoquinone until the second 1 mg. dose has been received. Further study is necessary to demonstrate such an assumption. As the vitamin K preparation was given to the infants orally and in some instances was not completely retained, this may be a factor in variations noted. Eight infants, 4 per cent of this group, showed curves decreasing to 30 per cent of normal clotting activity or below.

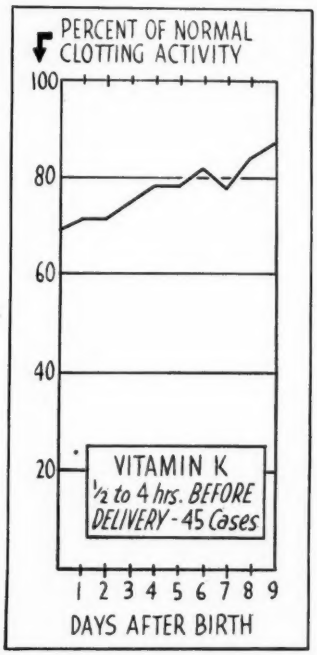

Fig. 7.—The effect of vitamin K given one-half to four hours before delivery.

Vitamin K During Labor.—The third group studied consists of 117 infants whose mothers were given the vitamin K preparation during labor. A single dose of 4 mg. of 2 methyl-1, 4 naphthoquinone in capsules was given to the patient upon admission to the labor room. Again the dosage was empirically established and was kept at a constant level. The composite curve for these infants is shown in Fig. 6. It is to be noted that no drop occurs in the clotting activity of this group. Of this group of infants 3.4 per cent showed a level of 30 per cent or less of normal clotting activity. Forty-five patients in this group received the vitamin K preparation one-half to four hours before delivery. Surprisingly the curve for this group of infants (Fig. 7) is not unlike that for the total group. Eight of these patients received the vitamin K two hours or less before delivery, and in this group the protection is incomplete but does not appear to be completely absent. It must be borne in mind, however, that some of the untreated infants show little or no drop in prothrombin clotting time, and our series is too small to

warrant conclusions in this connection. It is quite obvious, however, that vitamin K administered during labor, without previous medication during the prenatal period, is effective in preventing a drop in prothrombin levels during the neonatal period.

DISCUSSION

Our investigation covers the period from September 1, 1939, to August 5, 1940. During this period repeated observations have been made on 506 infants. There were, in addition, 15 stillborn infants and 9 infants who died during the neonatal period. This represents a gross fetal mortality of 4.5 per cent. Of the 9 infants who died during the neonatal period, 2 received vitamin K subsequent to delivery, 4 were born of mothers who received vitamin K during labor, and 3 were in the control group. In 2 of these 9 infants a clinical diagnosis of cerebral hemorrhage was confirmed at necropsy. The mothers of each of these infants had received vitamin K during labor. In the first case (XC-39592) a hydrocephalic infant with a lumbar spina bifida was delivered by low forceps application and extraction. Death occurred forty-two hours after birth, following frequent attacks of cyanosis, impaired respiratory activity, and convulsive movements. Necropsy showed a fracture of the frontal bone and extensive intracranial hemorrhage. The second infant (XC-40921) was delivered naturally following an episiotomy after a forty-hour labor. Respirations were spontaneous and the infant appeared in good condition. A cyanotic attack with difficult respiration occurred twenty-two hours after delivery, and the infant died at thirty-nine hours. A prothrombin determination following the initial evidence of cerebral irritation was 50 per cent of normal. Two milligrams of the vitamin K preparation were given by gavage nine hours before death. Necropsy showed an intracranial hemorrhage as the cause of death. In neither of these infants are we justified in assuming that a low prothrombin level in the blood was a factor in the intracranial hemorrhage. In the first case there was obvious trauma, and in the second infant the clotting activity was not significantly impaired.

Details of the case histories of the two infants have been cited to show that one is not justified in expecting miracles from the use of vitamin K. It is well recognized that the production of a normal clot is only one of the factors in the control of hemorrhage. The permeability and fragility of the capillaries must also play an important role. It seems a fair assumption that trauma will continue to be the predominant cause of intracranial hemorrhage in the newborn. It is, however, a logical assumption to add the statement that an infant subjected to some degree of injury may fail to develop a significant hemorrhage unless a marked decrease in the prothrombin level of the blood is present. Similarly, a mild hemorrhage may become marked as the physiologic decrease in prothrombin develops forty-eight to seventy-two hours subsequent to delivery. From this standpoint, the administration of a vitamin K preparation during the early neonatal period or, perhaps, preferably during labor, should afford some increased protection to the infant.

TABLE I. INFANTS WITH CLOTTING ACTIVITY BELOW 30 PER CENT

DAYS AFTER BIRTH	NO VITAMIN K %	VITAMIN K DURING LABOR %	VITAMIN K AFTER DELIVERY %
0	1.1	None	1.5
1	11.5	0.8	4.0
2	19.2	1.7	1.0
3	19.7	3.4	2.0
4	9.8	None	None
5	6.5	2.5	None
6	2.2	0.8	None
7	1.6	None	None

In Table I are listed the percentage of infants in each of the three groups we have studied whose clotting activity decreased to 30 per cent or less of normal. It will be seen that the vitamin K preparation is remarkably effective from a prophylactic standpoint by either plan of administration. With some adjustment in the dosage and in the time of administration of the preparation, a complete prevention of the decrease may be anticipated. From study of our data we would suggest that administration of 4 mg. of 2 methyl-1, 4 naphthoquinone at an interval greater than two hours before delivery, will prevent a significant decrease in the prothrombin level of the blood in more than 95 per cent of infants during the neonatal period. We would also suggest that all infants whose mothers have not received vitamin K at an interval greater than two hours before delivery should receive 1 mg. of 2 methyl-1, 4 naphthoquinone at intervals of six and twenty-four hours following delivery. We would further suggest that all infants subjected to a prolonged labor or difficult delivery receive a vitamin K preparation during the early days of the neonatal period.

The relationship of vitamin K to hemorrhagic disease of the newborn is now well established. The early reports of Brinkhous, Smith, and Warner,[10] Waddell, Guerry, Bray, and Kelley,[21] and of Nygaard[22] as well as the recent publications by Quick and Grossman,[23] and Poncher and Kato[24] leave little doubt that hemorrhagic disease of the newborn is a hypoprothrombinemia and that vitamin K is a specific therapeutic agent.

During the period of our study we have encountered no typical case of hemorrhagic disease of the newborn. There have, however, been 7 infants in whom various hemorrhagic tendencies have become manifested. Without exception, these infants have shown a level of clotting activity below 10 per cent of normal. The hemorrhagic manifestations have included bleeding from the cord stump, vomiting of blood-streaked mucus, and the passage of bloody mucus through the rectum. In two instances convulsive movements were also present. In no infant have similar hemorrhagic tendencies developed in the absence of a low clotting activity of the blood. All of this group responded to the administration of 2 methyl-1, 4 naphthoquinone by a prompt increase in the clotting activity and a cessation of the hemorrhagic tendencies. Fig. 8 illustrates the typical curve of such an infant. This infant (XC-39002) vomited a blood-tinged mucus on the third and fourth days following delivery. One milligram of 2 methyl-1, 4 naphthoquinone was given orally on the

fourth day when the clotting activity was 10 per cent of normal. It had risen to 38 per cent in four hours. A second 1 mg. was given on the fifth day. A reading later on the same day was 84 per cent, and the clotting activity remained within normal limits. There was no further evidence of bleeding.

Such a group of infants offers confirmatory evidence for the statement that hemorrhagic disease is due to a prothrombin deficiency. It is true, however, that infants may show a similar prolonged low level of clotting activity without any evidence of hemorrhage. Such curves were shown earlier in the discussion. Perhaps infants in this group should be looked upon as subclinical cases of hemorrhagic disease. Perhaps there is some other factor necessary to precipitate the hemorrhage.

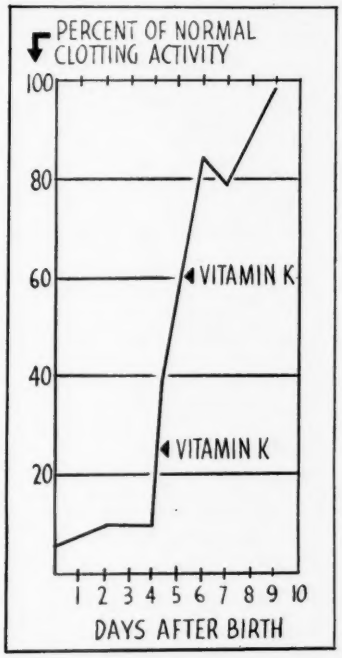

Fig. 8.—The therapeutic effect of vitamin K in hypoprothrombinemia.

SUMMARY

A study of the clinical records combined with laboratory data concerning the clotting activity of the blood of 530 newborn infants confirms the previously reported observation that there is a physiologic decrease in prothrombin activity during the early days of the neonatal period.

The prevention of this decrease by the administration of a vitamin K substance has been investigated.

A simple clinically applicable test for the rapid assay of the clotting activity of the blood has been presented.

CONCLUSIONS

1. Normal infants show a physiologic decrease in prothrombin activity in the blood which reaches a maximum during the third day of life.

2. A spontaneous return to a normal level occurs during the first week of life.

3. A wide variation is noted in individual infants in the depth of this decrease and in the rapidity of the return to normal levels.

4. This decrease in clotting activity can be prevented by the administration of a vitamin K preparation to the infants during the early hours of the neonatal period or to the mother during the course of labor.

5. A potential relationship exists between the level of prothrombin activity in the blood and the severity of intracranial hemorrhage.

6. There is a direct correlation between spontaneous hemorrhagic tendencies in the newborn and a low prothrombin activity in the blood.

7. 2 methyl-1, 4 naphthoquinone exhibits an active vitamin K effect.

The vitamin K preparation, 2 methyl-1, 4 naphthoquinone, has been generously furnished by E. R. Squibb & Sons.

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1040-1232 N. MICHIGAN STREET

BREECH DELIVERY*

ELMER M. HANSEN, M.D., LINCOLN, NEB.

THE subject of breech presentation has been discussed in the literature frequently during the past decade. Articles have appeared upholding both the conservative and active management of this presentation, but to date there has been no significant change in the fetal mortality. One is impressed with the fact that the results depend to a great extent upon the ability of the operators to perfect their particular method of treatment.

Most of the communications on this subject have come from large obstetric centers representing, to a great extent, clinic material. The material used as a basis for the presentation of this communication represents the cases of breech deliveries occurring in the associated practice of Dr. Harold S. Morgan and myself over a period of twelve years. It is not a large series of cases, but it represents, we believe, an experience which is comparable to that of the average obstetrician in private practice, and for this reason, we are presenting this series of cases.

During the past twelve years, 1,882 patients were delivered. One hundred and twenty-six babies were presented by the breech, the incidence being 6.7 per cent. This is higher than that usually reported. The incidence of breech presentation during the past twelve years at the Lincoln General Hospital in which 90 per cent of our patients were delivered was 4.2 per cent. Our increased incidence is explained by the fact that a large number of complicated deliveries are referred to us by general practitioners doing obstetrics. The parents of these babies are all white, coming from all social levels, chiefly middle-class American, the foreign element being negligible. The 126 babies were delivered of 120 mothers; four mothers had twin pregnancies in which both babies were presented as a breech, and 2 mothers had breech presentations in two succeeding pregnancies. There were 73 primiparas and 53 multiparas.

SOURCE OF CASES

Hospital	*Deliveries*	*Breech*
Lincoln General	1,719	114
Bryan Memorial	118	9
St. Elizabeth	45	3
Total	1,882	126

Incidence	6.7%	No. of mothers	120
	Primiparas	73	
	Multiparas	53	

*Presented before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

DURATION OF LABOR

(Variation)

	Primiparas	*Multiparas*
1st stage	2½ to 57 hours	1 to 31 hours
2nd stage	5 min. to 7¼ hours	5 min. to 2 hours

(Average)

1st stage	12.6 hours	6.3 hours
2nd stage	1.2 hours	35.1 min.

13 primiparas had 2nd stage over 100 minutes.
1 multipara had 2nd stage over 100 minutes.

FETAL ATTITUDE

Ninety-six of the breech presentations were frank breech, 25 were single footlings, and 13 were double footlings. Sixteen of the single and 4 of the double footlings occurred in premature deliveries.

Duration of Labor in Primipara.—The first stage averaged twelve and six-tenths hours, varying from two and one-half hours to fifty-seven hours. The second stage averaged seventy-one minutes, varying from five minutes to seven hours and seventeen minutes. There were 13 patients who had a second stage of over two hours' duration.

Duration of Labor in Multipara.—The first stage averaged six and three-tenths hours, varying from one hour to thirty-one hours. The second stage averaged thirty-five minutes, varying from five minutes to two hours. Only one multipara had a second stage over one hour and forty minutes.

TYPE OF DELIVERY

Manual Aid	*Extraction*	*Section*
109	13	4
5 decomposed (1 forcep)	2 forceps	
7 forceps		

The type of delivery is divided into three groups: manual aid, the procedure to be described, extraction, and cesarean section. One hundred nine patients were delivered with manual aid. In 5 of these, the breech was decomposed and then the patient delivered with manual aid. Forceps were applied to the aftercoming head in 7 patients.

Extraction was the treatment in 13 patients. In 3 instances the patient failed to make progress in the second stage and extraction was the procedure then indicated. In 2 of these patients, forceps were applied to the aftercoming head. Two patients had late toxemia of pregnancy, and it was deemed best to terminate the delivery when the cervix was dilated. Two patients, both of whom were multiparas with placenta previa, one with a dead baby, were delivered through the placenta. Six premature twin babies were footling presentations, 2 being the first baby and 4 being the second baby of twins.

Cesarean section was done on 4 patients. Two patients had section for placenta previa, and the breech presentation was incidental. Two patients, both elderly primiparas, were delivered by elective section because they had large babies and it was thought that delivery from below was questionable.

Prolapse of the cord did not occur in the entire series.

FETAL MORTALITY

126 deliveries

15 babies died	Rate 11.9%
5 multiparas	Rate 9.4%
10 primiparas	Rate 13.7%

Period of Gestation	*Abnormality*	*Weight*
Term	None	8 lb. 4 oz.
Term	Spina bifida, hydrocephalus	7 lb. 14 oz.
34 weeks	Anencephalia	5 lb. 4 oz.
27 weeks	Premature	1 lb. 14 oz.
27 weeks	Premature	2 lb. 10 oz.
26 weeks	Premature	2 lb. 12 oz.
25 weeks	Premature (toxemia)	2 lb. 5 oz.
24 weeks	Premature (second of twins)	1 lb. 7 oz.
28 weeks	Premature Twins	1 lb. 9 oz.
28 weeks	Premature Twins	1 lb. 10 oz.
33 weeks	Premature (No fetal heart tones) Placenta previa	4 lb. 15 oz.
28 weeks	Premature Twins	2 lb.
28 weeks	Premature Twins	1 lb. 10 oz.
27 weeks	Premature Twins	1 lb. 7 oz.
27 weeks	Premature Twins	1 lb. 8 oz.

Summary of Fetal Mortality

Term:

1 Intracranial hemorrhage
2 Monsters

Premature:

1 33-week placenta previa. Stillborn.
No fetal heart tones on admission.

11 period of gestation, 24 to 28 weeks.
Weight varying from 1 lb. 7 oz. to 2 lb. 12 oz.

Corrected mortality 0.8 per cent

Fifteen babies were stillborn or died neonatally. This gives a gross mortality of 11.9 per cent. Five deaths occurred in multiparas (9.4 per cent), and 10 in primiparas (13.7 per cent). Eleven babies were definitely premature, the period of gestation ranging from twenty-four to twenty-eight weeks, and the weights varying from 1 pound 7 ounces to 2 pounds 12 ounces. Several were one or both of twins. One baby was of thirty-three weeks' gestation, and the mother, a multipara, had central placenta previa and no fetal heart tones on admission. Three patients were at term. One normal baby, weighing 8 pounds, 4 ounces, was delivered by manual aid after a second stage of five hours. The baby lived eight hours and fifteen minutes, and died suddenly. Post-mortem examination revealed intracranial hemorrhage and a large cephalohematoma. One baby was hydrocephalic with a large spina bifida; it did not cry and lived only a few minutes. The third full-term baby was an anencephalic monster. Excluding the premature and abnormal babies, there remains only one fetal death or a corrected incidence of 0.8 per cent.

FETAL MORBIDITY

One baby who presented a frank breech was delivered by extraction after spontaneous delivery of the umbilicus because both arms were extended. The baby required resuscitation. Inspection revealed marked asymmetry of the face, with a depression of the vault into which the forearms fitted. This baby had bilateral Erb's palsy when delivered. The right arm recovered in seven days and the left arm in three weeks. The left clavicle was fractured during delivery. One other baby had a fractured clavicle. Three babies developed cephalohematomas, and several babies developed hematomas of the sternocleidomastoid muscle. They all developed after the patient left the hospital. No known serious sequelae followed.

TWINS

Twin incidence was interesting. In our series of breech presentation, 8 babies were one of a set of twins; one of these died of prematurity. Eight babies represented both babies in 4 sets of twins. Six of these babies died. In the twelve years

we have delivered 17 sets of twins, or 34 babies. Sixteen babies were breech presentations; seven of the 16 died, all of prematurity. Eighteen babies were cephalic; two of these died of prematurity.

MATERNAL MORTALITY

None

MATERNAL MORBIDITY

Twelve Cases *Incidence 9.52%*

CASES	CAUSE	METHOD OF DELIVERY	MATERNAL COMPLICATIONS	DURATION	SEVERITY
1	Phlebitis	Section		6 weeks	Severe
1	Pyelitis	Manual aid	Previous cystitis	4 days	Mild
1	Otitis media	Manual aid		4 days	Mild
1	Cystitis	Section	Placenta previa	2 days	Mild
1	Parametritis	Extraction		5 days	Mild
1	Unknown	Manual aid		2 days	Mild
1	Unknown	Bag induction Manual aid	Toxemia	2 days	Mild
1	Unknown	Section	Placenta previa	3 days	Mild
1	Unknown	Manual aid		2 days	Mild
1	Unknown	Manual aid		2 days	Mild
1	Unknown	Section		3 days	Mild
1	Unknown	Manual aid		2 days	Mild

There was no maternal mortality. There were 12 mothers who had a temperature of 100° F. on two succeeding days, excluding the first twenty-four hours post partum. There were 122 confinements, which gives an incidence of 9.8 per cent. Causes of morbidity could not be determined in 7 patients. These were all mild and lasted only two to three days. In 5 patients the cause was known. One patient had phlebitis of the left lower extremity. She had had an elective section. She was in the hospital six weeks and recovered. One patient, with a previous history of pyelitis had a flare-up lasting four days. One patient had acute otitis media lasting four days. One patient with cystitis of two days' duration was delivered by section because of placenta previa, and one patient with a parametritis (tender uterus) had mild symptoms for five days. All 4 patients delivered by section were morbid, but the morbidities were mild, with the exception of the case of phlebitis.

DISCUSSION

The diagnosis of breech presentation was made prenatally in practically every patient coming for prenatal care. Routinely, we carefully check our measurements and estimate the size of the baby. If there is a question of fetopelvic relationship, we use the x-ray as an aid to our decision. External version was not attempted in any patient.

Our method of treatment is conservative. By conservative treatment, we mean giving supportive treatment to the mother with no interference unless labor is obstructed, progress ceases, or complications arise endangering the life of mother, baby, or both.

We were trained in the watchful expectancy method, and from experience we are convinced that meddlesome interference is a definite factor in the difficulties encountered in obstetrics. I am sure that if we all agree that conservatism is good procedure in cephalic presentations it should be rational in the breech.

From personal observation and experience, we have formulated the following points to guide us in breech delivery:

1. Dilatation of the cervix does not become complete in many cases until the buttocks are presenting deeply at the introitus.

2. Attempted delivery before complete dilatation is almost certain to result in extension of arms and head with difficulty in delivery.

3. It is natural for the force to be applied from above. Application of force from below by traction is not the normal force. Extension of the arms, nuchal arms, and extended head are the result of force applied from below rather than from above.

4. Manipulation from below, especially if the patient is not deeply anesthetized, will reflexly stimulate tetanic contraction of the cervix or lower uterine segment; this contraction imprisons the shoulders and cephalic pole in the uterus and delays delivery; it also necessitates increased force which traumatizes both mother and baby.

5. Gentleness in all maneuvers is of the greatest importance.

CONCLUSION

We have reported a series of 126 breech deliveries occurring during twelve years of private practice, with a corrected fetal mortality of 0.8 per cent.

Conservative treatment in our hands has produced satisfactory results. Teamwork is an important feature of our treatment, and we believe it has had a definite influence on our results.

Prematurity, especially prematurity in twin pregnancy, accounted for 80 per cent of our fetal deaths. Efforts toward preventing premature labor in twin pregnancies should lower the gross fetal mortality of breech presentation.

This communication deals with private practice only. The reporting of many similar analyses and comparing them with reports from the clinic groups, we believe, would be worth while.

128 North 13th Street

DISCUSSION

DR. DAVID L. SMITH, Indianapolis, Ind.—The staff of the University Hospital at Indianapolis is essentially a closed one, made up of members of the teaching staff. There are two and one-half ward patients to one private patient. There were 190 breech presentations in 1,264 deliveries. Of the 31 stillbirths 4 were monsters, 6 were macerated fetuses and 6 were premature. There were 11 deaths attributable to the breech presentation, so the corrected mortality was 5.78 per cent, which is a great deal higher than Dr. Hansen's. I have no way of accounting for that difference, except possibly on the basis that our service is somewhat of an emergency service, being a state hospital which admits patients from all over this portion of the state who have received no prenatal care and who sometimes are desperately ill.

Review of the charts sometimes leads to conclusions as to what not to do. Two of the deaths occurred in labors which had been induced, both of which were definitely past term by history. In both the babies weighed a little over 5 pounds. One of the cardinal principles in breech management is to avoid induction of labor.

We believe in external version as long as it is done with gentleness and without anesthesia. We personally have been successful in external version in about 60 per cent of the trials. Cesarean section should probably play a greater part in the management of breech delivery.

We use intermittent nitrous oxide and oxygen anesthesia, and then change to drop ether at the time the umbilicus is born. We are using forceps on the aftercoming head more and more because we believe it is less traumatic to the baby than any other method of delivery.

DR. IRVING F. STEIN, Chicago, Ill.—A complete breech is one with the fetus in the attitude of complete flexion, and the incomplete breech is one of deflexion attitude. I do not believe that this has been emphasized in obstetric literature. In incomplete breech one frequently observes the fetus in a military attitude with the head erect or sometimes turned to the side or even tilted back, like an inverse brow presentation. A greater amount of mobility of the fetus is evident with breech than with cephalic presentation. Even with complete breech you may occasionally find a displaced arm and the head a little deflexed; this can be discovered only by x-ray examination. The practical application of this procedure enables you to be forewarned and prepare for manual aid or extraction.

The points I wish to emphasize are first, that incomplete breech is an example of a deflexion attitude; second, in cases of breech particularly, you can obtain much practical information by taking roentgenograms before delivery which would otherwise be missed by ordinary methods of examination.

DR. RUDOLPH W. HOLMES, University, Va.—Some 75 years ago Carl Braun reported in his textbook on 67 cases of face presentation which were seen in his clinic. He stated as a result of that great experience that a face presentation in a primiparous labor was *prima facie* evidence of a pelvic deformity.

In our more mature knowledge of pelvic abnormalities we now know that pure pelvic asymmetry is as potent a cause as is definite contraction. We may further state that the flat pelvis and the obliquely contracted types are more prone to produce malpositions and presentations than the symmetrical generally contracted pelvis.

Not only is a face presentation produced by these factors, but we may broaden that statement to the rule that all deviations of presentation are sequential to aberrant contours of the pelvic brim. In my own experience a breech delivery with a *normal* pelvis is as physiologic and as safe as the normal vertex positions. On the other hand, when there is any disproportion, the breech delivery is fraught with the greatest difficulty and danger.

I still believe that it is the exceptional case of breech which demands a cesarean section. Contributing factors which are of etiologic importance may more often indicate cesarean operation than similar conditions in a vertex position.

DR. R. S. SIDDALL, Detroit, Mich.—I want to make a few remarks on the basis of a recent monograph which Dr. Seeley and I have published. We found in going over a considerable number of papers in the literature that there were several series of 100 or 150 cases in which the results were comparable with those of Dr. Hansen. We did not find, however, any series of 200 or over which did not have a very considerable increase of fetal, not maternal, deaths associated with breech.

In our series from the Herman Kiefer and Harper Hospitals in Detroit it was noticeable, however, that we would often have 125 or 150 cases in a series with only one or two deaths. Although one may have a relatively small series with good results, one eventually encounters difficulty.

External version is associated with very little danger. It is very reasonable to employ an easy and safe procedure to convert a dangerous presentation associated with from 5 to 20 per cent mortality into one with only 1 or 2 per cent mortality.

We found that there were three things which contributed very largely to excessive fetal mortality in breech: (1) The mortality increases with babies weighing from 8 pounds to 9 pounds and over until it reaches 20 to 25 per cent. (2) Elderly primiparas have a "lamentable" fetal mortality, as someone expressed it in the literature. It may be around 25 to 30 per cent. (3) Contracted pelvis also has a high mortality, even in the minor grades of pelvic contraction.

DR. A. F. LASH, Chicago, Ill.—As a result of an extensive experience at the Cook County Hospital in Chicago, where we deliver over 5,000 babies a year, there are certain points which are crystallized in our minds regarding breech delivery.

First, breech presentations can deliver spontaneously as well as cephalic. This point requires special emphasis because when we get into discussions with the doctors in the surrounding rural communities, they say, "How can we deliver these babies without getting a 90 per cent fetal mortality?" Too often the conception is that as soon as the presenting part is visible, immediate extraction is started and it is associated with complications.

Second, with regards to analgesia, we feel that we want the cooperation of the patient throughout labor. We never use the barbiturates during the first stage. If the patient is in strong labor and requires some rest, we feel morphine and scopolamine fulfill that requirement. Pudendal block and local infiltration of the perineum and pelvic floor will allow complete cooperation of the patient which helps in the delivery of the baby.

We do not feel that eight minutes between the appearance of the cord and the delivery of the head is so important. We have found that as much as fifteen minutes can be taken in the delivery of the head as long as air reaches the mouth by retracting the perineum. It is at this point that the greatest harm is done to the baby by undue traction. When we feel that the head seems to meet with a good bit of obstruction, instead of continuing the extraction we usually release our pull on the baby's head; we push the baby up, which allows increased flexion of the head, bringing the head down in the transverse diameter, thereby facilitating delivery of the head. With this in mind, I think we avoid damage to the baby and lower our fetal mortality.

DR. FREDERICK H. FALLS, Chicago, Ill.—Breech is more common in the arcuate type of bicornate uterus, which is seen relatively frequently. When breech is present in such a uterus, it is very difficult or impossible to do external version, and I think it is often dangerous even to try. We feel that not infrequently a combination of arcuate type of bicornate uterus and breech is a relatively strong indication for cesarean section. Since adopting this policy, we have had very much better results in this type of case.

In placenta previa we frequently have an associated breech presentation, because under this circumstance the breech will fit the lower uterine segment better than the head. The combination of breech and placenta previa is also a relative indication for cesarean section.

The importance of the fact that the premature baby frequently presents by the breech cannot be overemphasized. The more premature the baby is, the more reason there is for thoroughly dilating the birth canal. In these cases we thoroughly dilate the birth canal and do an episiotomy to avoid cerebral damage to the premature baby during delivery.

DR. J. C. LITZENBERG, Minneapolis, Minn.—If you will change the term "external version" to "attempted external version" you will avoid a lot of arguments. I have always taught that external version should be attempted but I have never persisted in it if it offers any difficulties whatsoever. There are certain conditions in which it should never be attempted. It is a shame in a case where external version could be done with the greatest of ease not to do it, but it is also a shame, and a greater one, to persist in its use when one has difficulty.

DR. E. M. HANSEN (closing).—Dr. Morgan and myself have always tried to be conservative in our estimation of our ability to do a good job delivering a breech, and I am very frank with you when I say there has been a question in my mind as to just how much luck we have had in our series. As time has gone on each breech presentation has been a very definite challenge to us, and I think in that respect this challenge has had a very definite influence on our work, because we have tried every time to get a live baby.

With regard to external version, not once was it attempted. The reason for this is that in my period of training I saw many external versions attempted and but very few of them successful. On two occasions babies were lost, one with pre-

mature separation of the placenta and another with rupture of the membranes, and prolapse of the cord. Before the situation could be analyzed, the baby died. Also, we have had unusually good results in the series without doing external version.

In answer to Dr. Stein: We do not maintain forcible but a steady fundal pressure so as to control, if possible, the flexion of the aftercoming head.

Four patients had cesarean section, two with placenta previa and the breech presentation was incidental. The other two were elderly primiparas. One was 43 years old, having her first baby, which weighed over 9 pounds. The other primipara was 38 years old and delivered a baby which weighed 9 pounds, 15½ ounces. I believe that these are real indications. As it is, our incidence of cesarean section is very low.

I would like to say a little something about the general practitioner and his treatment of breech presentation. A few years ago we investigated the fetal mortality in our hospitals, and there was one hospital in our state that had a fetal mortality rate of 33 per cent in breech presentation over a period of three years. At the Lincoln General Hospital where we have done most of our work, we have a set of rules regarding our obstetric department. No man, and it makes no difference whether he is a member of the obstetric staff or a visiting man who brings in a patient for delivery, can do an operative delivery and that includes breech extraction, without consultation. It is his privilege to call in a member of the obstetric department for consultation, which service must be rendered free of charge. Under the influence of that rule our fetal mortality was lowered to one-third of what it had been for the previous five years. It has now been in effect for approximately five years. The general practitioner usually interferes. It would be preferable for him to be more conservative.

ARE THE ANTERIOR PITUITARY-LIKE SUBSTANCES GONADOTROPIC?*

A Clinical Evaluation in the Woman

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THE anterior pituitary-like substance from human pregnancy urine has been available for clinical use during the past decade. However, the medical literature is not unanimous in its opinion regarding the physiologic effects of this material. The well-known gonadotropic response obtained in the mouse and rabbit is not found consistently throughout laboratory animals, nor has it been duplicated in the human female in any manner that will stand critical evaluation.

The clinical reports in the literature are based on patients who were treated for some menstrual abnormality of uncertain etiology and unpredictable course. On the basis of such observations, many authors enthusiastically recommend its use, but here and there are reports of dissenting opinion.

Geist[1] described atretic follicles with hemorrhage in women treated with antuitrin-S. Rock[2] described probable degeneration of follicles in women following its use. Hamblen[3] called attention to premature and increased involutional changes

*Presented before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

in ovaries of treated women. Eisenstaedt[4] and others[5] have described various apparently noxious changes in the testis resulting from the use of P.U. extract in treatment of cryptorchidism.

The present study was arranged to determine by clinical experimentation whether the anterior pituitary-like extracts of pregnancy urine have any demonstrable effect on the human ovary. The physiologists and the pharmacologists select normal animals under standard experimental conditions for testing drugs. This investigation was carried out along parallel lines by studying first the effect of antuitrin-S on the normal ovary, then on the abnormal.

In hoping to approximate ideal experimental conditions for clinical research, we considered the following factors as basic requirements for any satisfactory interpretation of results. (1) The group of patients should be fairly large and live in a uniform environment. (2) They should be of good health, similar age and past reproductive history. (3) They should have an accurate menstrual record for twelve months prior to study, and during an observation period of at least six months following treatment. (4) Since it is impossible to make observations of the ovary itself, endometrial biopsies should be taken at frequent intervals, as they offer conclusive objective information regarding ovarian activity. While Bartelmez[6] and a few others have found several stages of endometrial development in a single uterine specimen taken during menstruation, it is well established[7] that the rhythm of the endometrial histology parallels the ovarian cycle and indicates the functional state of the ovary.

To fulfill these experimental requirements most satisfactorily, the patients should be institutionalized during the course of the investigation; those of the Ypsilanti State Hospital were made available to us for study. Patients with a normal menstrual rhythm during the previous year of hospitalization were examined, and 12 were selected who had no palpable pelvic abnormality, who were fairly stationary in regard to their psychoses, and who met all the above requirements. Most of these patients were multiparas; this supports our findings of an essentially normal generative tract. A second group of patients with a hospital record of at least twelve months' amenorrhea were also examined, and 7 were selected for study. Since no apparent cause for the amenorrhea could be found on clinical examination of these patients, amenorrhea was thought to be due to the psychosis.

Endometrial biopsies were taken with the Novak suction curette at frequent intervals before, during, and after treatment; a total of 143 endometrial samples were obtained from 19 patients. Menstrual records were kept throughout the period of treatment and for several months after the cessation of treatment. One cubic centimeter (500 R.U.) of antuitrin-S* was administered daily for four or six weeks. Even though this is a larger dose than is used clinically, except in unusual cases, no untoward local or systemic reactions were noted in

*Antuitrin-S was freshly manufactured material furnished through the courtesy of Parke, Davis & Co.

these patients. In order to determine whether the physiologic activity of antuitrin-S is predominantly follicle-stimulating or luteinizing, some of the patients were treated in each phase of the cycle; namely, after the menstrual period (follicular phase) and just after the midinterval (early corpus luteum phase).

The normal menstrual and endometrial rhythm was not appreciably altered in 7 (58 per cent) of the 12 patients. Fig. 1 abstracts the records of 4 of these subjects. On the basis of endometrial histology it appears that C. R. had an anovulatory cycle just preceding and again during treatment. Antuitrin-S in the dosage given did not cause ovulation or corpus luteum formation in this case, although there was a slight irregularity in the subsequent menstrual rhythm. Another patient, M. W., skipped a menstrual period one month after treatment. This suggestion of an induced amenorrhea is more apparent in the menstrual histories of the patients in Fig. 2. Five (42 per cent) of the 12 patients treated experienced a temporary amenorrhea of from one to five months. Endometrial biopsies taken in the early stages of this amenorrhea are characterized by a resting endometrium, suggesting a suppression of follicular maturation.

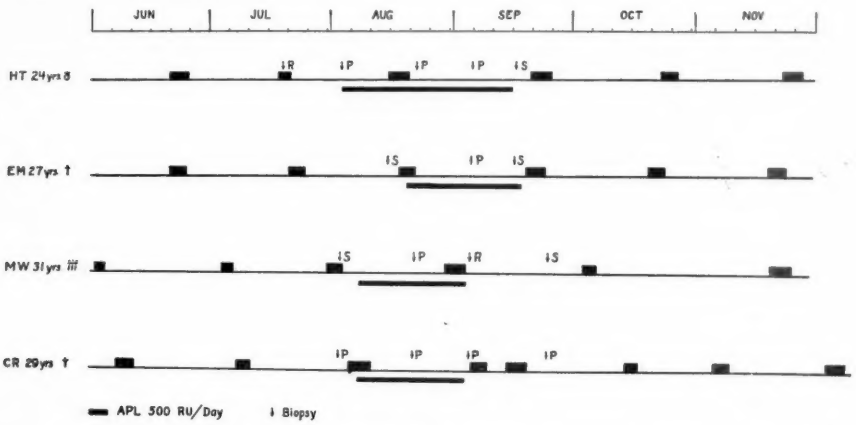


Fig. 1.—Effect of antuitrin-S on women with normal menstrual cycles. Note: C. R. had an anovulatory cycle before and during treatment.

The patients with an unexplained amenorrhea of one or more years' duration were studied in a similar manner. A first-voided morning specimen of urine was concentrated by the alcohol precipitation method of Zondek, as modified by Frank,[8] and was assayed for pituitary gonadotropic hormone. The test was negative in each instance, indicating the patient had not gone through a premature menopause. This was verified by the subsequent return of menses in 4 of these patients. The dosage of antuitrin-S was the same in this group as in the normal patients, 500 R.U. daily for four weeks. Two controlling biopsies were taken before treatment.

The first 2 patients in Fig. 3 are excellent examples of the unpredictability of the return of menstruation. In each case a normal menstrual period occurred during the two weeks' observation period before treatment was started, even though they had had nineteen months and twelve months of amenorrhea, respectively. Treatment was started on M. B. on the day of the second biopsy and was continued even though menstrual function was re-established. In view of the amenorrhea induced in normal patients, it is interesting that this patient (M. B.) had only 2 menstrual periods,

while the patient who was not treated (A. B.) continued to have regular menstrual cycles. The other patients shown in Fig. 3 did not menstruate as a result of treatment, and the endometrial biopsies give no indication of any increased ovarian activity. An attempt was made to get twenty-four-hour urine specimens for estrogen assay before and during treatment. Due to the inability of the patients to cooperate in this portion of the study, the results can be considered as suggestive only. The findings that were obtained failed to show any change in estrogen excretion during treatment.

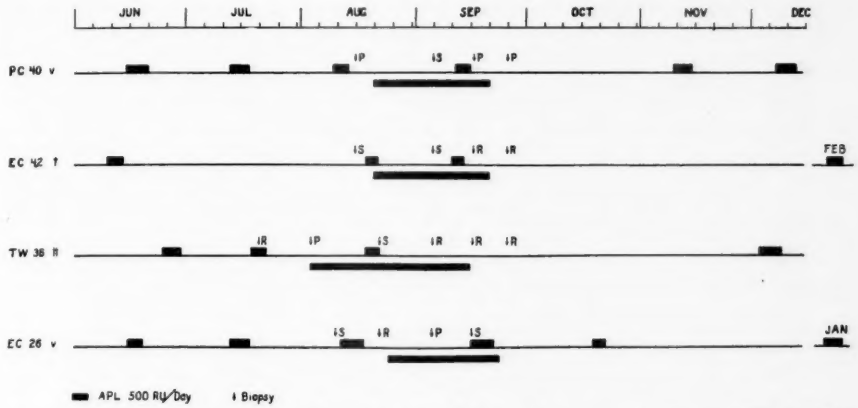


Fig. 2.—Temporary amenorrhea induced in 5 of 12 (42 per cent) women with regular cycles by antuitrin-S.

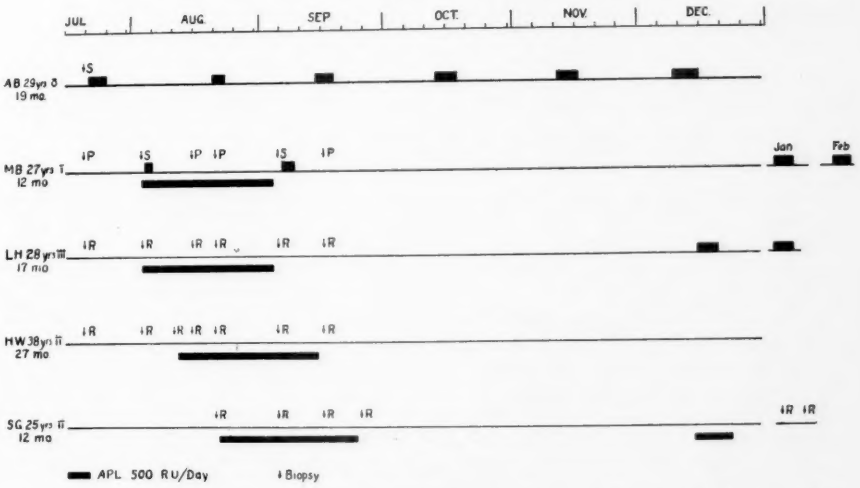


Fig. 3.—Patients with unexplained amenorrhea treated with antuitrin-S. Note: Two patients, A. S. and M. B., resumed menses during period of observation, and M. B. had a three months' amenorrhea following antuitrin-S treatment.

Having obtained these results, we instituted a second period of treatment on a small group of patients to see whether the findings of the original series could be duplicated and to obtain more detailed information on the condition of the endometrium during and following treatment by a study of a more complete series of biopsies. Antuitrin-S (500 R.U. daily) was given to 3 normal and 3 amenorrheic patients for six weeks, and biopsies were taken once a week for twelve weeks.

The records of these patients are charted in Fig. 4; the patients restudied may be identified by their initials and ages in the previous figures. E. C. previously had a three months' amenorrhea following treatment but in this study she skipped March; her April bleeding was anovulatory. E. M. had previously shown no effect but in this series she developed an anovulatory period in March, and in April no endometrium could be obtained; she skipped her May period. C. R. had an anovulatory period in both the first and present series, and as indicated, this was followed by an amenorrhea of five months. Again the deviation from the normal following antuitrin-S therapy is a tendency toward an induced anovulatory bleeding or amenorrhea. The patients with an unexplained amenorrhea were not benefited by this treatment.*

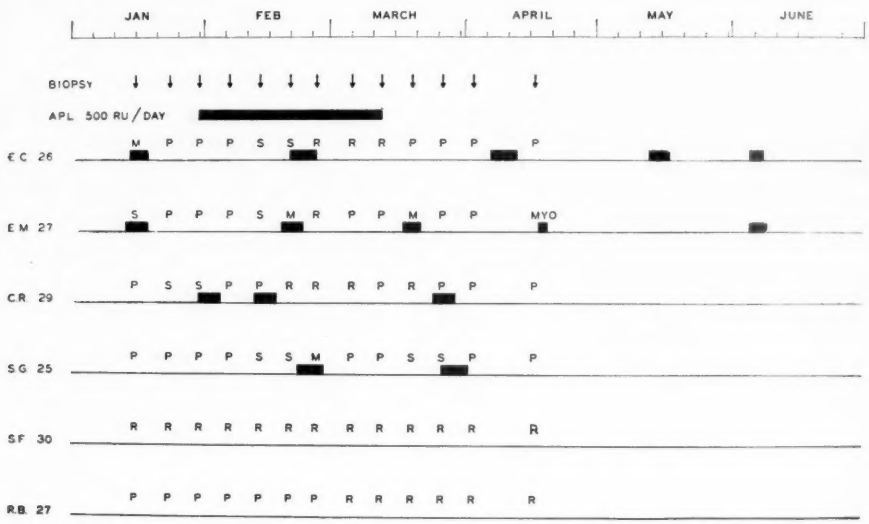

JAN
FEB
MARCH
APRIL
MAY
JUNE
BIOPSY
APL 500 RU / DAY
E C 26
M P P P S S R R R P P P P
E M 27
S P P P S M R P P M P P MYO
C R 29
P S S P P R R R P R P P P
S G 25
P P P P S S M P P S S P P
S F 30
R R R R R R R R R R R R
R B 27
P P P P P P P R R R R R R

Fig. 4.—Late effect of antuitrin-S on endometrium of menstruating and amenorrheic patients (see also footnote).

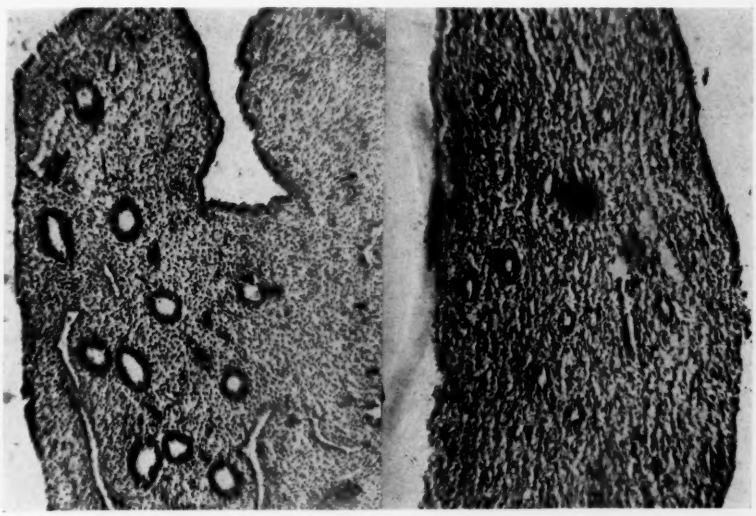
As the period of treatment entered the fifth week, it became increasingly difficult to obtain any endometrium from the patients, and frequently only portions of the basalis or myometrium were found. The endometrium showed a progressive atrophy that approached the menopausal state. The atrophy is evident in the biopsies shown in Fig. 5. Antuitrin-S apparently suppressed ovarian function to such an extent that the secretion of estrin was reduced and the endometrium atrophied. This suppression of follicular maturation in the human ovary is similar to the findings of Engle[9] and Smith,[10] who report a definite follicular atresia and suppression of estrogenic hormone in the monkey by anterior pituitary-like substances. Their work is of interest since the monkey has a menstrual cycle very comparable to that of woman.

Since a daily dose of 500 R.U. did not produce any significant alteration of the menstrual cycle in the majority of patients, a dose of at least twice this amount would be necessary to induce consistently an amenorrhea by the suppression of ovarian activity. The lack of any stimulative effect at the dosage used in this study makes it seem probable that the published reports of correction of menstrual abnormalities during treatment with doses of 100 to 500 R.U. per week are coincidental rather than treatment effects.

In view of this demonstrated suppression of ovarian activity, there would be no indication for the use of the anterior pituitary-like sub-

*S. G. was having a remission from her psychosis during March and April and was being paroled for short visits at home. The occurrence of these 2 menstrual periods was undoubtedly more closely linked with her improved mental state than with coincident therapy.

stances in ovarian hypofunction. The apparent success of antuitrin-S in some cases of functional bleeding can be more satisfactorily explained as the result of a suppression of ovarian follicles, so that the endometrium is relieved of a prolonged estrogenic stimulation. A total dose of 8,000 R.U. over a period of two weeks produced a four months' amenorrhea in one of our patients who had been bleeding continuously for eight months.



A. *B.*

Fig. 5.—Endometrial atrophy produced by antuitrin-S (same magnification). *A*, 1/30/40 before treatment; *B*, 3/5/40 two weeks after treatment. Note: See Fig. 4, EM.

SUMMARY

Twelve patients with a normal menstrual rhythm were given 500 R.U. of antuitrin-S daily for four or six weeks. The majority of these patients did not show any significant alteration in rhythm. Five (42 per cent) experienced an amenorrhea of from one to five months following treatment. This induced amenorrhea was accompanied by a progressive atrophy of the endometrium, indicating a suppression of ovarian follicles.

Antuitrin-S failed to establish uterine bleeding in patients with amenorrhea. No evidence of ovulation or luteinization, as demonstrated by a secretory endometrium, was found.

On the basis of this experiment it appears that the anterior pituitary-like substances are not gonadotropic in the human female and in sufficient dosage may even be gonadotoxic.

We wish to express our indebtedness to Parke, Davis & Co. for furnishing the material used in this study and for financial support which made possible the technical assistance of Miss Helen McRae. We also wish to take this opportunity to thank Dr. Yoder and his staff for their cooperation and permission to use their patients; and especially, Marie Dahl, R.N., who gave the treatments and supervised the care of the patients during this study.

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DISCUSSION

DR. JAMES T. BRADBURY, Ann Arbor, Mich.—Dr. Brown has presented evidence that the human ovary is suppressed rather than stimulated by the anterior pituitary-like substance from human pregnancy urine. His evidence for follicular suppression is based on the definite involution of the endometrium which was observed during treatment. This is in accord with the observations of Engle on the monkey, where it was shown that this A.P.L. substance caused a follicular atresia and a diminished production of estrogen. There was no evidence of any luteinizing activity in this series of patients since, judging from the endometrial histology, at least five of them failed to form an active corpus luteum during the period of treatment and the life of the corpus luteum was not prolonged in any instance. Having failed to demonstrate either a follicle-stimulating or a luteinizing effect, both of which have been claimed for A.P.L., it may be well to evaluate the evidence upon which these effects have been established.

The present concept of the gonadotropic function of A.P.L. is largely based on the changes in the ovary of an immature rat or mouse that has been treated for ninety-six hours and then autopsied. At that moment the picture is one of ovarian stimulation and precocious maturity. However, when these animals are allowed to survive, the majority of them have been found to be sterile. When newborn female rats and mice are treated, they are all rendered permanently sterile. This induced sterility is not part of the usual concept of a gonad-stimulating substance. The detrimental end results of treatment may change the interpretation of the apparent stimulative effects seen in the Aschheim-Zondek reaction. Even the immediate effects of this anterior pituitary-like extract are not consistent in different animals. The guinea pig ovary does not show any stimulative effect. The field mouse does not respond at any dosage, and the deer mouse responds only when massive doses are given. A more prolonged treatment in guinea pigs, or in newborn rats and mice, leads to definite masculinization and sterility.

In view of these inconsistent responses of the different animals, it appears that the Aschheim-Zondek reaction upon which the usual concept of follicle-stimulating and luteinizing effects is based is an atypical reaction. A broader analysis of the situation indicates that A.P.L. is more frequently a depressor or an inhibitor of ovarian function.

With this experimental background it is obvious that the clinical findings presented by Dr. Brown represent another instance of the inhibiting effect of A.P.L. on the ovary. This substance excreted in the urine of pregnant women is elaborated by the placenta, but its purpose or function is still a matter of conjecture. It certainly plays no part in the physiology of the nonpregnant woman, so that it is not surprising that it has so little demonstrable action on the human ovary.

It is well known, however, that A.P.L. is gonadotropic in the male for it stimulates the testis to produce male hormone and may even accelerate spermatogenesis. This fact does not make a valid argument that it should also stimulate the ovary. The best evidence shows that A.P.L. is most frequently an inhibitor of ovarian function and, for that reason, we have suggested that A.P.L. is gonadotoxic rather than gonadotropic as far as its effect on the human ovary has been demonstrated.

PITUITARY EXTRACT FOR DYSTOCIA DUE TO UTERINE INERTIA IN THE FIRST STAGE OF LABOR*

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(From Herman Kiefer Hospital and the Division of Obstetrics and Gynecology, Wayne University)

THE early employment of posterior pituitary extract, in large doses, as an oxytocic resulted in such serious accidents as to bring about condemnation of its use in labor before delivery of the child. Williams, in referring to pituitary extract in uterine inertia, says, ". . . its administration is reprehensible during the first stage of labor." Titus agrees with this, without qualification, except to include the second stage as well. "However," to quote Faber and Mussey, "it remains a fact that many competent practitioners in rural and outlying communities have continued its use in smaller doses than were used originally, with a fair measure of success, often obviating the necessity for operative termination of labor under conditions decidedly unfavorable." Inquiry will quickly show that such use is not confined to outlying communities but indeed is practiced to an extent in some large clinics here and abroad (DeLee, Gavaudan). In our opinion the fact that large doses are undoubtedly highly dangerous does not necessarily mean that small quantities of the substance should be so harmful as to be totally contraindicated. For some years now at Herman Kiefer Hospital, pituitary extract in small doses has been given in selected cases where stimulation of inefficient labor pains would be of great advantage. The present investigation was undertaken to indicate the results, both as to efficiency and dangers, of such use in prolonged labors due to weak labor pains.

The patients studied were those with prolonged labor (thirty hours or over) in whom pituitary extract was given in the first stage of labor for weak pains, and in whom:

1. There was definite evidence that true labor had begun.
2. Inefficiency of labor pains, or uterine inertia, was apparently the chief or only cause of dystocia.
3. Delivery occurred at term of a single child weighing 2,500 Gm. (5 pounds 8 ounces) or over.
4. The child was alive when pituitary extract was started.
5. There was no fetal anomaly or any complication seriously jeopardizing the fetus, such as prolapsed umbilical cord or toxemia of pregnancy.
6. There was no major interference in labor before pituitary extract was given.

Limitation of cases to those which were in accord with the foregoing criteria appreciably reduced the number available for study. However, this exacting selection seemed necessary in order to assure as nearly as possible a clear-cut consideration of the effects and results of pituitary

*Presented at the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

extract, alone and free of other factors, in dystocia during the first stage of labor due to uterine inertia. The largest group of records eliminated were those with obvious or possible doubt as to the existence of actual labor when the substance was given. By accepting only the patients with obliteration of the cervical canal and beginning dilatation of the external os, as well as regular though weak labor pains, it seems probable that false conclusions due to the inclusion of any substantial number of simple inductions of labor or false labors were largely obviated. Reasons are obvious, we believe, for the other restrictions upon acceptance of cases into the studied series.

During the five-year period preceding December 31, 1939, a total of 62 patients were delivered at Herman Kiefer Hospital, whose labors conformed to the criteria given. Thirty-seven were delivered of their first children, and 25 had had one or more previous full-term or premature deliveries. As shown in Table I, occurrence of the different fetal positions approximated the usual distribution.

TABLE I. DISTRIBUTION OF PATIENTS IN REGARD TO FETAL POSITION

POSITION	PRIMIPARAS	MULTIPARAS	TOTAL
O.L.A.	17	16	33
O.R.A.	6	6	12
O.L.P.	2	0	2
O.R.P.	11	3	14
Breech	1	0	1
Total	37	25	62

The substance used was principally the solution of the oxytocic principle of the posterior pituitary lobe (pitocin) in a strength of 10 international units per cubic centimeter. In some instances the extract of the whole lobe in obstetric strength (10 international units per cubic centimeter) was given, and here, as seems to be generally conceded, there was no apparent difference in the oxytocic activity of the two preparations. The substances were given hypodermically in doses twenty to thirty minutes apart, beginning with 1 to 3 minims and increasing a minim with each dose up to a maximum of 5 minims. The course was discontinued at the point where good stimulation of uterine contractions occurred; or where there was little effect, after 5 or 6 doses. The fact that in 19 cases there was strong, and in one of these excessive, stimulation following initial injections of 2 to 3 minims suggests that for safety the first dose should perhaps be no larger than 1 minim. It also should be noted that in a few instances the administration of quinine preceded the pituitary extract, and in 5 instances artificial rupture of the membranes was done in association with the use of pituitary extract. For the sake of completeness, it is perhaps well to add that, in addition to the special measures outlined, these patients also received the usual supportive treatment, including intravenous glucose solution and rest periods induced by morphine or other sedative drugs as indicated. Tables II and III illustrate the stimulating effectiveness of the gland extract.

TABLE II. CASE EFFICACY OF SMALL DOSES OF PITUITARY EXTRACT IN STIMULATING FIRST-STAGE LABOR PAINS IN PATIENTS WITH PROLONGED LABOR DUE TO UTERINE INERTIA

STIMULATION OF PAINS	PRIMIPARAS	MULTIPARAS	TOTAL CASES
Slight or temporary	13	7	20
Moderate	4	2	6
Strong	18	13	31
Strong with artificial rupture of the membranes	2	3	5
Total	37	25	62

Table II shows that in 20 of 62 cases there was slight or temporary, and, therefore, for the most part negligible, stimulation of the labor pains. In 6 others there was only moderate effect, yet from a review of the histories it was evident that the stimulated pains persisted and caused sufficiently progressive dilatation of the cervix as to consider the effect of the extract to have been definitely helpful or even satisfactory. In the next group of 31 the pains became strong and continued so until completion of the first stage. Though the last group is small (5 cases), it may be significant that in all these patients with employment of pituitary extract plus artificial rupture of the membranes there resulted strong and lasting pains. In 42 of 62 cases, with first-stage dystocia and prolonged labor due to uterine inertia, there occurred moderate to strong stimulation of uterine contractions up to complete dilatation of the cervix. The proportions for primiparas and multiparas were approximately the same, being 65 and 72 per cent, respectively. In this series we failed to find any reasons or associated factors, other than artificial rupture of the membranes in 5 cases, to explain why or how the administration of a substance with only a short pharmacologic action could cause lasting stimulation of uterine contractions. Nevertheless, from the clinical standpoint it is an important observation that such action was actually obtained in a substantial majority of our cases.

Although Table II indicates successful stimulation of pains in approximately 2 of 3 of these patients, the result when obtained did not follow a single administration or course of injections in all patients. In 3 primiparas and 8 multiparas two separate series of doses, and in one multipara 4 courses, were required for satisfactory effect. It is also true that repeat courses of the extract were unsuccessful in 6 primiparas and 2 multiparas. In Table III are given the results for the 84 individual series of injections, 62 being initial and 22 subsequent courses after an elapse of several hours or more. In addition to parity, there is also a tabulation of efficiency according to the degree of dilatation of the cervix.

In Table III no striking difference is noted for administration in primiparas or multiparas, the effect being definitely helpful or satisfactory in about 50 per cent in both. Approximately the same results were obtained in the different stages of dilatation of the cervix, with the exception of advanced dilatation in multiparas, where success was obtained in all. Here, however, the number involved (5) was too small for a trustworthy conclusion.

The foregoing data give, we believe, at least a conservative estimate, and probably an underestimate, of the beneficial results to be obtained in hastening dilatation of the cervix from careful administration of pituitary extract in uterine inertia. One of our standards for acceptance of a patient into the series was that labor should be prolonged for at least thirty hours. This restriction was intended to make certain that

TABLE III. STIMULATING EFFECT ON LABOR PAINS OF INDIVIDUAL SERIES OR COURSES OF PITUITARY EXTRACT INJECTIONS (INITIAL 62 AND REPEAT 22) IN PRIMIPARAS AND MULTIPARAS AND EFFECT ACCORDING TO DILATATION OF THE CERVIX

STIMULATION OF PAINS	PRIMIPARAS				MULTIPARAS				GRAND TOTAL
	CERVIX LESS THAN 3 CM.	CERVIX 3 TO 6 CM.	CERVIX 6 CM. PLUS	TOTAL SERIES OF INJECTIONS	CERVIX LESS THAN 3 CM.	CERVIX 3 TO 6 CM.	CERVIX 6 CM. PLUS	TOTAL COURSES OF INJECTIONS	
Slight or temporary	4	10	8	22	8	11	0	19	41
Moderate	2	0	2	4	2	1	0	3	7
Strong	4	10	4	18	2	7	4	13	31
Strong with artificial rupture of membranes	0	1	1	2	2	0	1	3	5
Total	10	21	15	46	14	19	5	38	84

only cases of true first-stage dystocia were included. At the same time, however, it eliminated a large number with originally poor pains in whom successful use of the substance had resulted in delivery before thirty hours, whereas those with poor results tended to go the time limit and were included in the study. Furthermore, a review of the 20 failures in the series showed that, though stimulation was reported as slight or temporary, there was better progress subsequent to the injections in a substantial number. Indeed, even in these so-called failures, operative intervention before full dilatation of the cervix was required in only 3 instances, i.e., introduction of a hydrostatic bag in 1, and incision of the cervix (Dührssen) in 2. Such interference was not necessary, of course, in the 42 where the extract gave moderate to strong and lasting stimulation.

Granting that pituitary extract is helpful in the majority of prolonged labors due to poor pains, there remains the paramount question as to whether or not its dangers are so great as to contraindicate use even in these difficult cases. In order to avoid the well-known risks of large doses for both mother and child, our patients were given small initial amounts so as to test out the reactivity of the uterine musculature, and subsequent doses as required were increased gradually. As noted before, we believe the first administration should perhaps not exceed 1 minim. Starting with 2 and 3 minims, a number of our patients (19) had strong pains immediately, though in only one was there excessive stimulation. After a 2 minim dose, this patient, a primigravida, had very strong and rapidly recurring uterine contractions with little relaxation. The alarming situation was relieved by the administration of ether anesthesia. Stimulation was only temporary, and fourteen hours later Dührssen's incisions and a midforceps delivery were done. Although there was no apparent damage done to mother or child, and although this is the only experience of the kind that we know of in this hospital, the incident shows that even a small dose is not free of all risk. The prompt effect of ether anesthesia in this instance, and on a similar occa-

sion which one of us experienced in another hospital, lends support to DeLee's advice that a can of ether and a mask be readily at hand in these cases.

A review of the mortality in this series showed that there was one maternal death. We had some doubt about including this patient in the study since she had a contracted pelvis. So far as the first stage of labor was concerned, however, dystocia was apparently due to uterine inertia rather than cephalopelvic disproportion. In any event, at 8 cm. dilatation of the cervix 2 doses of pituitary extract (2 and 3 minims) gave good stimulation of the weak pains, so that the cervix was soon fully dilated. Descent of the head in the second stage came to a standstill at the level of the ischial spines. Four hours later an unsuccessful attempt at forceps delivery was followed by a difficult podalic version. Then, extraction was impossible, and craniotomy was necessary. The patient was in shock after delivery, but death twenty-two hours later came so suddenly as to suggest the possibility of pulmonary embolus. Viewed retrospectively, it appears that craniotomy immediately upon failure of forceps extraction, rather than another procedure, might well have had a different outcome for this woman. Certainly, there seems to be no reason for believing that administration of pituitary extract was in any way responsible for the regrettable result.

There were 3 stillbirths (and no neonatal deaths) in this series, besides the one due to craniotomy just mentioned. Two deaths occurred in primiparas, the fetal heart sounds disappearing approximately three hours and five hours after the extract was given. In both of these cases there was only fair or moderate stimulation of pains. The third death was in a multipara who had good stimulation of the pains but showed no suggestion in the record of tetanic contraction of the uterus. The exact time of death was not definitely stated. Evidently, 3 of the 4 dead fetuses in this series cannot be reasonably attributed to the effect of pituitary extract. The most that can be said for the fourth is that it was possibly due to the procedure, though the resulting uterine contractions were apparently no stronger than those that often occur in normal labor. Whatever the causes of the deaths, it seems fair to say that the gross fetal mortality of only 6.5 per cent in this small series gives no definite evidence of increased risk from the administration of pituitary extract. Indeed, considering the fact that these were very difficult cases, it may be justifiable to say that the relatively low mortality indicates the reverse.

SUMMARY

Although large injections of posterior pituitary extract are admittedly dangerous when given in labor, this does not mean that small doses cannot be given with reasonable safety and advantage in prolonged first stage of labor due to poor labor pains. In 62 such cases (definitely in labor at term and with normal children) there was efficient and lasting stimulation of pains in 42. Five patients given pituitary extract plus artificial rupture of the membranes had good stimulation. Some patients

were given two or more courses of repeated doses, good results for the individual courses being about 50 per cent. This percentage was approximately the same for primiparas and multiparas and also for different degrees of cervical dilatation, except for 6 cm. or more dilatation in multiparas where there was good effect in all 5 instances. In this series of 62 very difficult cases, intervention before full dilatation of the cervix was required in only 3, these being among those with only slight or temporary stimulation. That the method is not entirely free of danger is shown by the fact that there was one case of tetanic contraction of the uterus after a 2 minim injection without detectable injury to mother or child. Because of this experience and for other reasons, we recommend that the initial dose be no larger than 1 minim. One maternal death followed difficult operative delivery *after* full dilatation of the cervix and was not ascribable to use of pituitary extract in the first stage. The child in this case was subjected to craniotomy. Three other babies died in utero, but with evidence pointing to difficult labor rather than use of pituitary extract as the cause. There were no neonatal deaths or diagnosable birth injuries in the 58 babies born alive.

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DISCUSSION

DR. DAVID S. HILLIS, CHICAGO, ILL.—There are two things that are very much needed in obstetrics. One is an efficient and safe way to induce labor. Another is some successful method to manage the prolonged labor case. Personally, I would prefer to deal with any other complication in obstetrics than with a cervix which will not dilate. This is regarded as such an important question at Cook County Hospital that all prolonged labor cases are assigned to one attendant who gives each case his personal attention in an effort to learn the best method of dealing with this type of dystocia.

This in my opinion is an honest and intelligent contribution to our knowledge of the subject. The old method of using sedatives alone in prolonged labor has proved to be most unsatisfactory in a certain large proportion of cases. It is quite natural to turn to pituitrin as a drug which is known to increase some uterine activity and is the only agent which does this in a positive manner.

Pituitrin has a bad reputation because of the fact that it was seriously abused for many years after its introduction to the profession. Unfortunately, there is still some abuse of pituitrin. However, it is about time for the medical profession to learn to use a powerful agent such as this in an intelligent and conservative manner. It is not right that the profession should be deprived of the useful effects of a drug, properly used, just because some members of the profession abuse its use.

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—I believe that pituitary extracts are highly dangerous to mother and fetus when injudiciously employed. Shortly after this drug became the obstetric panacea, it was exhibited promiscuously in heroic dosages with disaster. In those early days I collected 13 cases of uterine rupture in the Chicago area following the use of this drug, with the death of all

mothers and their babies. It is an inexcusable blunder to give full ampoule dosages to stimulate uterine contractions. Fractional amounts in selected cases may be of inestimable value. I believe Hofbauer's nasal administration is the preferable method, for if untoward signs begin to develop the nasal pledget may be readily removed.

In normal vertex presentations at the time "lightening" occurs, there is a fair contact between the head and the girdle of the lower uterine segment. As a result of this pressure a progressively increased intensity and frequency of contractions develops. When there is any interference with the adaptation of the presenting part, labor is almost always accompanied by weak, ineffectual contractions in the first stage. As example of such conditions I would cite pelvic assymmetry or contraction, abnormal presentations and placenta previo. All of these are accompanied by the classic ineffectual, nagging contractions, with a prolongation of the first stage, called by the earlier writers *dolores presagientes*. It is a difficult matter to differentiate between such false pains and the so-called primary inertia. Believing these precepts, I rarely used fractional doses of pituitrin to stimulate contractions during the early part of such labors. In selected cases the extract from the posterior lobe is of great value. Ordinarily, allowing the woman to change her position in bed, to walk about, and even giving her chloral hydrate and sodium bromide are of help. I have seen such fetal disasters follow the administration of morphia in labor with resultant prompt termination of labor that for years I had practically prohibited its use in my services.

In conclusion, I believe that Doctors Siddal and Harrel have shown a rare circumspection in employing those fractional doses of the pituitary gland extracts in a selected few distinctly abnormal cases culled from the large series of patients their clinic has attended. If their conservatism were general in the profession we would have no rabid strictures against the use of this indispensable drug. The use of it is invaluable, its abuse an abomination.

DR. GERALD W. GUSTAFSON, INDIANAPOLIS, IND.—It would be very interesting, particularly as this work was done in Detroit, to have Dr. Schreiber study these babies to find whether he could detect any evidence of areas of cerebral degeneration.

I believe there is only one real indication for pituitrin while the baby is still in the uterus, and that is in the treatment of the worst cases of abruptio placentae. A few years ago we all taught radical treatment for these cases. Last week in my service in the Indianapolis City Hospital we had a chance to see what conservative treatment could do. The woman was a para iii who came in in tremendous shock. After giving two or three transfusions, she was given 1 minim of pituitrin, the membranes were ruptured, a Spanish windlass was applied, and she went into labor. She delivered a stillborn baby normally. I was very skeptical about this particular type of treatment after hearing DeNormandie telling of their success in the Boston Lying-in Hospital, but I am convinced that many more mothers will be saved by its adoption.

DR. J. C. LITZENBERG, MINNEAPOLIS, MINN.—What type of syringe is used when you inject one minim of pituitrin?

DR. SIDDALL (closing).—We use a tuberculin syringe for giving pituitrin. I do not believe there is any other syringe by which you can accurately measure dosage.

Pituitrin has been badly abused and we do not want to repeat those instances. However, from our experience we still believe that the drug has a place in a certain number of cases. I cannot conceive our giving up the use of this aid in patients, such as those of this series, who really need its help.

THE RELATIVE EFFECT OF ANALGESIA AND ANESTHESIA IN THE PRODUCTION OF ASPHYXIA NEONATORUM*

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IN VIEW of the widespread use of drugs and anesthetics to relieve the pain of childbirth, not only by specialists but also by general practitioners as well, there has been an understandable critical scrutiny of the results of this practice. Since the introduction of barbiturates, there have been numerous papers which extol the benefits of these drugs either alone or in combination with scopolamine, but most of them deal only in general with results as far as the babies are concerned. Physicians have been taken sharply to task for predelivery medications by such observers as Henderson and Schreiber. Henderson,[1] for example, states that 30 to 60 per cent of babies delivered under analgesics are born asphyxiated and need some method of resuscitation, while Schreiber[2] states that as a result of asphyxia at the time of birth many babies suffer from permanent cerebral damage.

If these statements are borne out by further investigation, it will be obligatory for us to discontinue the use of sedatives. Recently, there have been investigations which have led us to believe that general anesthesia is also to blame for increasing the incidence of asphyxia of the newborn.[3]

In order to shed a little light on what is a seriously controversial subject, we undertook this investigation. Variables have been eliminated as far as possible. All deliveries were made by one of us (H. H.). These are consecutive deliveries over a period of about two and a half years. The analgesics used were sodium pentobarbital 3 to 6 grains, reinforced by scopolamine. In practically all instances enough analgesia was used to produce complete amnesia from the time the effect was produced until after the baby was born. In the local anesthesia 1 per cent novocain was used either by pudendal block or by perineal infiltration. A few of the more complicated deliveries were given intradural block. In the general anesthesia group drop ether was used in about one-half of the cases, and nitrous oxide and ether in the rest. The latter were given oxygen in sufficient quantity to keep the patient pink. The babies were all handled in the same way. After birth the child's air passages were cleared by milking the trachea and wiping out the mouth. No other stimulation was used. The cord was not cut until respiration was established or until definite asphyxia was diagnosed. If the child failed to breathe or gasped sluggishly, the air passages were cleared with a tracheal catheter and oxygen with 5 per cent carbon dioxide was given with an inhalator. Failing these methods, artificial respiration was then instituted.

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These two groups, then, eliminate the variables which can arise from difference in technique and training of the obstetrician. There always has been and still is a variation due to observation, and, for this reason, we established a classification of asphyxia different from that in common use.

We classify five groups of respiratory response as indicated in Table I. In this classification individual judgment is eliminated. Groups 1 and 2 can be classified as normal, while Groups 3 and 4 are definite asphyxia, differing only in degree.

TABLE I

Group 1.	Babies that breathe within ten seconds. These infants usually cry with the first expiration.
Group 2.	Babies that breathe between eleven and thirty seconds after birth. They also cry quickly as a rule.
Group 3.	The initial respiration is delayed thirty seconds or more. An infant which breathes earlier than thirty seconds and lapses into apnea is classed in this group. These babies are easily revived with tracheal catheter and oxygen.
Group 4.	Babies in whom the above measures fail and artificial respiration is necessary.
Group 5.	Stillborn.

We believe that this classification, at least for investigative purposes, is better than the division into asphyxia livida and asphyxia pallida. Both, it is true, are clinical classifications, but we feel that ours is the more exact. We also discarded the method of Cole, Kimball, and Daniels,[4] in which the degree of asphyxia was based on the number of methods of resuscitation used. As has been pointed out by others, a nervous operator may institute such measures earlier than a more phlegmatic obstetrician.

Many factors exist during labor which tend to produce asphyxia, and long before the advent of analgesia and anesthesia asphyxia neonatorum held a prominent place in the writings of obstetricians. Prolapsed cord, abruptio placentae, placenta praevia, dystocia, and occult cord pressure are conditions that are not completely under our control. Analgesia and anesthesia, however, are controllable. By painstaking observation and accurate reporting we can arrive at a formula which does not increase the hazard of birth.

All drugs and anesthetics must by their very nature cause depression of vital functions including the respiratory center. It is not our purpose to deny this. The amount and significance of this depression have been exaggerated by some and minimized by others. If reasonable relief of pain can be secured by medications now at our disposal, we are thoroughly justified in their use. If modification of our present methods of using these drugs will decrease the danger to mother and child, we must make these changes.

In this study all factors are considered which may increase the normal condition of mild asphyxia. Asphyxia values are arbitrary and undoubtedly erroneous in many cases, but in the aggregate they probably give a reasonably true estimate of their influence in the production of anoxemia.

We have assigned a minimal asphyxia value on spontaneous delivery, spontaneous breech, and prophylactic forceps. For the purpose of this paper, delivery by cesarean section has not been considered. Forceps delivery, versions and extractions, and breech extraction are assigned a high asphyxia value. The increase of asphyxia in prolonged labor and lengthy anesthesia has been shown graphically by Cole, Kimball, and Daniels, and this we have taken into account. Prolonged labor and anesthetics are similarly treated. We have considered analgesia in three groups: first, less than enough to produce full analgesia; second, full analgesia; and third, prolonged complete analgesia. Spontaneous onset of labor has a minimum asphyxia value. Medical induction is given an increased value and surgical induction a further increase. Bag induction is given the highest asphyxia value on account of increased cerebral pressure produced by this mechanical device.

Eastman has shown that the fetus lives in utero in a state of mild asphyxia.[5] There is no true arterial blood in the fetus. The fetal arterial blood has a lower oxygen saturation than the venous blood of the mother. This is partially compensated for by the higher oxygen carrying power of the newborn, since the average fetal hemoglobin concentration is 112 per cent while that of the mother is only 84 per cent.

TABLE II. OXYGEN SATURATION (AFTER EASTMAN)

MATERNAL BLOOD	%	FETAL BLOOD %
Arterial	95	63 (in utero) 50 (at birth)
Venous	71	20-25
No analgesia or anesthesia		

Snyder and Rosenfeld[7] showed that fetal respiration in utero is the rule and that these movements are not initiated at birth but are merely amplified with the result that air is introduced into the lungs at the birth of the child. Clifford and Irving[8] showed that these prenatal respiratory movements are slowed or stopped by the exhibition of certain drugs and anesthetics.

This new knowledge of the physiology of respiration has been generally accepted, although positive proof in the human being is still lacking. Accepting these findings makes us ask ourselves whether or not it is dangerous to the child to suppress these respiratory movements. If analgesia and anesthesia depress this function, their combined use should increase the incidence of asphyxia. As practical obstetricians we are loathe to give up analgesia, and the question arises in our minds, "What effect will the elimination of anesthesia have on the incidence of asphyxia?"

Clinically, analgesia does not decrease the oxygen content of the mother or the fetus. Patients are often restless, their pulse is elevated, and their skin is flushed, but they do not become cyanotic under doses that produce amnesia. Therefore, these drugs increase asphyxia by respiratory depression and not by intrauterine asphyxia. We believe then that barbiturates and scopolamine will not affect the oxygenation of the child as long as the placental circulation persists. If serious respiratory depression from drugs exists, then asphyxia will develop

as the placental circulation ceases. It is the object of this paper to throw some light on this question.

It might be well to recall at this point that the role of carbon dioxide in the stimulation of the respiratory center was the contribution of Yale's physiologist, Yandell Henderson, and it was he who first advocated use of oxygen-carbon dioxide mixtures to counteract this condition. Independently from this discovery, but almost simultaneously, the attitude of obstetricians changed from back slapping and hot and cold tubbing to one of gentleness and conservation of body heat, an attitude which today is more widespread and firmly grounded than ever.

Recently, Snyder and Rosenfeld showed that nonvolatile drugs, including all the commonly used analgesics, depressed or completely stopped intrauterine fetal respiratory movements. Similar findings were noted in nitrous oxide anesthesia, to a less extent following the use of ether, and not at all with cyclopropane.

In 1936 Eastman[6] published experiments indicating that chloroform has no appreciable effect on fetal oxygen concentrations, while ether reduced the saturation to 45 per cent in the arterial blood and to 15 per cent in the venous blood. Nitrous oxide-oxygen anesthesia shows an even greater reduction in the oxygen saturation of the fetal blood.

TABLE III. EFFECT OF ANESTHETIC ON OXYGEN SATURATION IN FETAL BLOOD AT BIRTH (AFTER EASTMAN)

	ARTERIAL %	VENOUS %
No anesthetic	50	20
Chloroform	No appreciable effect	
Ether	45	15
Nitrous oxide (80-20)	40	10
(90-10)	25	0.5

From the work of Snyder and Rosenfeld it appears that analgesics depress the respiratory center of the fetus but no proof is offered, and clinical observations indicate that drugs used in the first stage in moderate dosage have no effect on the oxygen saturation of the fetal blood. Anesthetics on the other hand, especially nitrous oxide, definitely lower the oxygen saturation of the fetal blood.

Little notice was taken of the possible late effects of asphyxia neonatorum until Schreiber called attention to a group of young children with late neurologic symptoms.[2] He reports that 70 per cent of a series of 500 cases showed some degree of apnea at birth. While he blames precipitate delivery, breech extraction, other forms of dystocia, and prematurity for many of these defects, he also indicts the use of analgesic drugs as a factor in the production of these late neurologic conditions. Whether one agrees with him in the entirety of his contentions or not, it makes us pause and re-evaluate our methods.

MATERIAL

In this report we have tabulated the results of 975 consecutive deliveries by one of us (H. H.), studying each case from the standpoint of all factors to which we may assign an asphyxia-producing value. Of these deliveries, 524 were made under varying degrees of analgesia plus whatever anesthesia was necessary to complete the delivery. A total of 451 babies were delivered under analgesia plus local anesthesia. The condition of the infant is tabulated in Table IV. Six and five-tenths per cent of all babies showed some degree of asphyxia, 90.6 per cent may be classified as normal, while 1.9 per cent were stillborn.

TABLE IV. SUMMARY OF ENTIRE GROUP

Total number of Cases		975	
Group 1	714 cases	73.2%	90.6%
Group 2	179 cases	17.4%	
Group 3	51 cases	5.2%	6.5%
Group 4	13 cases	1.3%	
Group 5	18 cases	1.9%	
90.6% show no asphyxia			
6.5% are asphyxiated			

When these figures are broken up into local and general anesthesia, we find that 95.4 per cent of the cases of those given local anesthesia were normal and 3.7 per cent were in a varying state of asphyxia. The asphyxia rate under general anesthesia is 9 per cent. Attention is called, however, at this point to the fact that the increase is entirely in the group of asphyxia livida (Group 3) because the incidence of Group 4 asphyxia is identical; namely, 1.3 per cent.

TABLE V. CONDITION OF INFANT AT BIRTH

A. General Anesthesia			
Total cases—524			
Group 1	361 cases	68.9%	88.3%
Group 2	102 cases	19.4%	
Group 3	40 cases	7.7%	9.0%
Group 4	7 cases	1.3%	
Group 5	14 cases	2.7%	
B. Local Anesthesia			
Total cases—451			
Group 1	353 cases	78.3%	95.4%
Group 2	77 cases	17.1%	
Group 3	11 cases	2.4%	3.7%
Group 4	6 cases	1.3%	
Group 5	4 cases	0.9%	

In Table VI the cases of asphyxia livida (Group 3) are analyzed. In the general anesthetic group of 40 cases there were possible etiologic factors noted in all but 13. When one remembers that occult cord pressure undoubtedly occurs frequently, this is not an unreasonable proportion. In the local group of 11 cases no cause is noted in 5 instances. Two cases are listed under aspiration of amniotic fluid. The possible effect of analgesia in producing this condition cannot be ruled out.

TABLE VI. SUMMARY OF CASES IN GROUP 3 (ASPHYXIA LIVIDA)

A. General Anesthesia (40 cases)	
No cause noted	13
Dystocia	7
Induction of labor	6
Coil of cord around neck	5
Prematurity	4
Partial premature separation of placenta	3
Breech	2
B. Local Anesthesia (11 cases)	
No cause noted	5
Partial premature separation of placenta	2
Aspiration of fluid	2
Pre-eclampsia (induction)	1
Prematurity	1

In Table VII the cases classed as Group 4 (asphyxia pallida) are analyzed. In the general anesthetic group of 7 no cause is noted in 5. One case terminated in a midforceps operation and one was complicated by a long induction in a nephritic toxemia, with no analgesia and a minimum of anesthesia. In the local anesthesia group we find a partial premature separation of the placenta, a tight coil of cord around the neck, a breech delivery, a midforceps operation, and a case of aspiration of amniotic fluid. The sixth case was noteworthy. The patient had a previous cesarean section and when labor began had a fulminating pneumonia. She was sectioned under sodium pentothal and abdominal block anesthesia. She died within twenty-four hours with complete consolidation of both lungs. The baby, however, was resuscitated and at present is living and well.

TABLE VII. SUMMARY OF CASES IN GROUP 4 (ASPHYXIA PALLIDA)

Total number of cases		13
General Anesthesia	7	
No cause noted		5
Midforceps		1
Nephritic toxemia		
Bag induction		
No analgesia		1
Minimum anesthesia		
Local Anesthesia	6	
Fatal maternal pneumonia		1
Sodium pentothal and local abdominal block		
Midforceps		1
Partial premature separation of placenta		1
Breech delivery (aspiration of fluid)		1
Tight coil of cord around neck		1
Aspiration of amniotic fluid		1

Table VIII classifies the stillborns. The data are self-explanatory and the only case needing clarification is the one listed as general hypoplasia. This child at post mortem showed craniotabes and a general lack of development, which probably accounted for its death. The heart was beating when born, but there was no attempt at respiration despite the exhibition of stimulants and artificial respiration. It is noteworthy that among these 18 cases there were none which could be classified as deaths resulting either from delivery or from the use of analgesic or anesthetic drugs.

TABLE VIII. SUMMARY OF CASES OF GROUP 5 (STILLBORN)

Total number of cases	18	
Macerated fetus		5
Monstrosities		5
Fetal heart lost early in labor (cord pressure?)		3
Premature separation of placenta		1
Erythroblastosis		1
Extensive placental infarction		1
Craniotabes and general hypoplasia (autopsy)		1
Premature (26 weeks)		1

The cases of local anesthesia were further broken down into, first, those receiving insufficient analgesia to produce amnesia; second, those receiving full analgesia; and third, those receiving heavy doses of analgesia. Full analgesia was considered as being 6 grains of nembutal and 2 one-hundredths to 3 one-hundredths grain of scopolamine. An amount less than this is called analgesia degree one; an amount greater is designated as degree three.

Table IX lists the cases of mild and extreme analgesia. It must be noted that the cases of analgesia degree three were long, hard, complicated labors. Yet as the table indicates there was essentially no difference in the condition of the babies at birth.

Inasmuch as the general anesthesia group shows a somewhat higher incidence of asphyxia than does the local group, the question arises as to the effect of operative procedures. Under pudendal block or infiltration anesthesia, it is difficult

TABLE IX. LOCAL ANESTHESIA

A. Analgesia degree 1 (mild)			
Total cases	40		
Condition of baby			
Group 1	22	73.3%	96.6%
Group 2	7	23.3%	
Group 5	1	3.3%	
B. Analgesia degree 3 (extreme)			
Total cases	53		
Condition of baby			
Group 1	37	69.8%	96.2%
Group 2	14	26.4%	
Group 3	1	1.9%	
Group 5	1	1.9%	

TABLE X. CONDITION OF BABY FOLLOWING OBSTETRIC OPERATIVE PROCEDURE OTHER THAN PROPHYLACTIC FORCEPS AND SPONTANEOUS BREECH DELIVERY

A. General Anesthesia (122 cases)			
(1) Midforceps 39 cases			
22 cases	Group 1	56.4%	84.6%
11 cases	Group 2	28.2%	
4 cases	Group 3	10.4%	13.9%
1 case	Group 4	2.5%	
1 case	Group 5	2.5%	
(2) Breech extraction and version 79 cases			
52 cases	Group 1	66%	90%
19 cases	Group 2	24%	
6 cases	Group 3	7.6%	7.6%
0 cases	Group 4	0	
2 cases	Group 5	2.4%	
(3) Dührssen's incision and forceps or version 4 cases			
2 cases	Group 1		
2 cases	Group 2		

TABLE XI

B. Local Anesthesia (62 cases)			
(1) Midforceps 32 cases			
28 cases	Group 1	87.5%	93.8%
2 cases	Group 2	6.3%	
1 case	Group 4	3.1%	3.1%
1 case	Group 5	3.1%	
(2) Breech extraction and version and extraction 25 cases			
20 cases	Group 1	80%	96%
4 cases	Group 2	16%	
1 case	Group 4	4%	4%
(3) Dührssen's incision and forceps or version 5 cases			
2 cases	Group 1		
2 cases	Group 2		
1 case	Group 5		

to do hard obstetric operations, and many of our complicated cases were given ether or nitrous oxide-ether for this reason. Table X lists a total of 122 cases in which major obstetric procedures were done, together with the incidence of asphyxia. Table XI shows 62 cases of dystocia delivered under local anesthesia. Table XII summarizes this information, with a comparison of the results in the entire group.

TABLE XII. SUMMARY OF CASES OF DYSTOCIA

	Entire group (524 cases)			Dystocia only (122 cases)		
A. General Anesthesia						
Group 1	361	68.9%	88.3%	76	62.3%	88.6%
Group 2	102	19.4%		32	26.3%	
Group 3	40	7.7%	9%	10	8.2%	9%
Group 4	7	1.3%		1	.8%	
Group 5	14	2.7%		3	2.4%	
B. Local Anesthesia						
	Entire group (451 cases)			Dystocia only (62 cases)		
Group 1	351	78.3%	95.4%	50	80.6%	93.6%
Group 2	77	17.1%		8	13.0%	
Group 3	11	2.4%	3.7%	0	0.0%	3.2%
Group 4	6	1.3%		2	3.2%	
Group 5	4	0.9%		2	3.2%	

SUMMARY

A series of 975 consecutive unselected deliveries by one operator are analyzed from the standpoint of factors which might produce asphyxia in the newborn. A slight preponderance of deliveries under general anesthesia was noted. Of the entire group 90.6 per cent required no resuscitation. Five and two-tenths per cent were revived simply by aspiration of the trachea and the administration of oxygen and 5 per cent carbon dioxide. One and three-tenths per cent required artificial respiration, and 1.9 per cent were stillborn. None of the 18 stillbirths could be attributed to the means of delivery or the use of either analgesics or anesthetics.

A total of 95.4 per cent of those in the local anesthesia group and 88.3 per cent of the general anesthesia group breathed spontaneously. Severe asphyxia occurred in the same percentage in the entire series; namely, 1.3 per cent. The chief difference between general and local anesthesia lies in Group 3 (asphyxia livida).

Reasonably definite causes of the asphyxia can be shown in about two-thirds of all cases of delayed respiration other than the exhibition of analgesics or anesthetics.

Among the local anesthetics there was no difference in the respiratory response whether analgesia was insufficient to produce amnesia or whether it was prolonged beyond the degree usually found sufficient to result in amnesia in the average normal labor.

In this series dystocia by itself apparently had no influence on asphyxia.

CONCLUSIONS

1. Ninety and six-tenths per cent of babies born when the mother is under the influence of analgesia show no evidence of clinical asphyxia.

2. Causes other than the use of analgesia or anesthesia are found in two-thirds of the cases that are clinically asphyxiated and may be present in others.

3. General anesthesia definitely decreases the respiratory response of the newborn.

4. The percentage of asphyxiated babies of amnesic mothers delivered under local anesthesia is comparable to the percentage expected when unnarcotized mothers are delivered under light ether or chloroform anesthesia.

5. When properly supervised and in the hands of those familiar with their use, analgesics per se do not increase the incidence of asphyxia.

6. Neither anesthesia nor analgesia, properly controlled, need be a factor in the production of stillbirths.

7. In the majority of cases asphyxia neonatorum is due to interference with the transfer of oxygen from the maternal blood to that of the fetus.

8. The use of local anesthesia whenever possible will reduce the natural hazard of birth.

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DISCUSSION

DR. GERALD W. GUSTAFSON, Indianapolis, Ind.—For years we have known that certain conditions would produce anoxemia in the infant. Of these, compression of the cord and abruptio placentae are the most common, but with very hard pains anoxemia may also be produced. Here the circulation through the placenta is so seriously compromised and the interchange of gases rendered so difficult that the fetal blood cannot be oxygenated. Under this circumstance, analgesia and anesthesia may actually benefit the fetus by decreasing the anoxemia. The significance of fetal respiratory-like movement is not agreed upon by physiologists, since Windle of Northwestern believes that under normal physiologic conditions the fetus is apneic and only develops respiratory movements in the presence of anoxemia.

It is a well-known fact that in the presence of extreme anoxemia, living cells degenerate. Schreiber has called attention to the possibility that unpharmacologic dosage of analgesia may produce this degree of anoxemia in the brain. This subject is, therefore, of increasing importance to the obstetrician, and it is up to us to show that our methods of analgesia not only are not destroying babies but likewise are not permanently injuring them from a neurologic standpoint. In a recent paper, Dr. Garceau and I showed that many cases of cerebral spastic paralysis, where marked cerebral injury was present, breathed spontaneously at birth without clinical evidence of asphyxia.

Until more investigation is done, the obstetrician should practice and teach a middle ground of analgesia. It seems to me that Dr. Henderson has done just that, for only 53 of his 975 cases had what he describes as extreme analgesia. His stillbirth record of 1.9 per cent, or 18 cases, in 975 deliveries is excellent, the stillbirth record in the United States for 1936 being reported as 34 per 1,000. None of his stillbirths could be classified as resulting from delivery or from use of analgesia or anesthesia. That 90.6 per cent of his babies breathed within thirty seconds indicates very little anoxemia in the entire group. Our experience with

block anesthesia, though small, coincides with his, since babies from mothers having block anesthesia breathe a trifle sooner than those delivered by general anesthesia.

My personal preference has been to supplement 6 grains of nembutal when necessary with rectal ether instead of scopolamine. In slightly more than 1,000 private cases using this method, no stillbirth attributable to analgesia has occurred.

DR. GEORGE KAMPERMAN, DETROIT, MICH.—All of us in Detroit were put on the defensive by the work of Schreiber, when he pointed out that damage to the brain could occur by anoxemia, and we could not refute the argument. That is one of the reasons why Dr. Henderson has undertaken this work.

I have not used much local anesthesia. I have practically given up nitrous oxide and have resorted to the use of ether when we do need an anesthetic. I believe that the ordinary anesthetist when she gives nitrous oxide is quite apt to give too little oxygen. We specify that we want 20 per cent oxygen, but the anesthetist often gives less, I am sure. It is hard for the operator to know just how much oxygen the patient is receiving.

As Dr. Gustafson said, I think the middle of the road in analgesia is still the proper thing. Personally, I think we should train our patients not to expect a painless labor. We should not tell them we will meet them at the front door with an analgesia. They should expect to go through part of the labor before analgesia is given. In this way a minimum of analgesia is needed to relieve the patient. Most patients can cheerfully endure the early labor pains. If we delay giving analgesia until dilatation of the cervix has well started, then usually one dose will carry the patient through the remaining labor. The amount that is given is exceedingly important.

DR. CHARLES EDWIN GALLOWAY, EVANSTON, ILL.—Since the world began about 2 per cent of the population has been born mentally deficient, and for someone to go into an institution and pick out several hundred cases and make the statement that the majority of them did not breathe very well at birth is not very scientific evidence that asphyxia is the cause of the brain injury. I discussed a paper concerning this subject when it was read in San Francisco and I am still of the same opinion. Apparently there is not much ill effect to either mother or baby when it comes to the matter of trying to relieve the pain of labor. I investigated all cases in my own community and asked each pediatrist and every psychiatrist whether analgesia in labor had anything to do with the mental deficiency of the children. We could not discover one case of mental deficiency in a child which could be attributed to the use of drugs at birth.

Each time an advance is made in the practice of medicine, certain problems have to be met. We are now trying to work out some of these problems. There are a few men among us who would much prefer to toss the problem out the window rather than to try to reach a solution. For instance, in the case under discussion, it is no solution to this problem simply not to administer drugs or anything to relieve the patient's pain. We should do as Dr. Henderson has done—work it out. If a baby is asphyxiated, then counteract the asphyxia immediately. We should strive to practice conservative medicine by administering only enough drug for pain relief and not too much as some physicians are now doing.

It is interesting to note that some of the men who are disparaging the use of analgesia are the very ones who have advocated it for years; they have even shown themselves in motion pictures administering morphine and scopolamine for their teaching. I believe that obstetricians all over the country are trying to relieve the pain of childbirth and that the individual obstetrician should not be discouraged, but rather encouraged, to continue on a rational basis with his effort.

DR. HENDERSON (closing).—Local anesthesia with moderate sedation can be used by the general practitioner, but as employed in this series it is undoubtedly inapplicable to the man who does an occasional case. Not once in the series given local anesthesia was there a serious post-partum hemorrhage; only one patient vomited, and this was due to fundus pressure when a large pair of shoulders impeded delivery. The patients all reacted more quickly than when general anes-

thesia was used. However, the patients are frequently restless, and it takes a trained hospital personnel to carry out the technique properly.

Dr. Galloway brought out the point that 2 per cent of all babies are born mentally deficient whether they have analgesia or not. Anoxemia may be a factor in these 2 per cent, but congenital defects of the brain and encephalitis acquired after birth, without doubt, account for many of them.

Dr. Schreiber has at least brought to our attention the possible danger of anoxemia, and this paper indicates in what way we may reduce asphyxia in the newborn without losing the desirable effects of carefully controlled analgesia.

CONGLUTINATIO ORIFICII EXTERNI AS A FACTOR IN DELAYED LABOR*

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ACCORDING to Gugisberg and Kraatz (cited by Katsu[1]), the incidence of the condition known as conglutinatio orificii externi is from 0.1 to 0.2 per cent; Zweifel (also cited by Katsu) found only 20 cases in the medical literature prior to 1873. On the other hand, this complication of labor is by no means as infrequent as it is generally supposed, for I have personally seen 3 cases in the last nine years, 2 of which occurred within the last eighteen months.

A survey of the medical literature has revealed only 28 articles on this subject from 1859 to date. All but 2 (Himmelsbach,[2] 1904; Porter,[3] 1910) are in the foreign literature, and most of these consist of only a few pages, devoted chiefly to case reports. The condition is mentioned briefly in Williams'[4] and DeLee's[5] textbooks, but most other textbooks of obstetrics ignore it completely. For this reason, I feel justified in calling attention to cervical conglutination as a possible cause of delayed labor and in putting on record 3 typical cases.

In order to comprehend the basic pathology of this condition, it is necessary to recollect the normal anatomy of the cervix. The outer longitudinal layer of muscle, which covers the uterine corpus and fundus, the broad, round, ovarian, and uterosacral ligaments, and the Fallopian tubes, stops short of the cervix. The cervical musculature consists chiefly of circular and oblique bundles, intermingled with a considerable amount of dense fibrous and elastic tissue, the structure accounting for the resistance and hardness typical of the cervix (Piersol[6]). When cervical conglutination is present, a few of the circular fibers around the external cervical os fail to dilate, although the effacement of the cervix, which is part of the physiologic process of labor is complete. They become thinned out by the bulging intact membranes or the advancing head, and the presenting part is separated from the vaginal canal only by a thin layer of cervical tissue, but they do not dilate and dystocia necessarily results. It is obvious, however, that the condition is not a true conglutination, as it was once believed to be, and that it should be given a new and more correct name.

*Read at the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

Although cervical conglutination, according to the reported cases, may occur in either primiparas or multiparas, it does not tend to recur in subsequent pregnancies. In certain instances the cause of the condition is clear; in others it is entirely speculative. The various causative factors established or suggested include:

1. The effect of the performance of plastic or mutilating operations upon the cervix.
2. The effect of the use of topical cervical applications or of corrosive substances, either for douches or in the attempt to produce an abortion.
3. Stenosis of the cervix following difficult labor.
4. Ulceration and induration as the result of syphilitic infection of the cervix.
5. Adhesions of the membranes about the internal os, with resultant prevention of the free action of the dilating fibers.
6. A predominance of fibrous tissue in the structure of the cervix.

Although the cause of cervical conglutination is not always clear, the clinical effects are always characteristic. In the usual case the position and presentation offer no obstacles to delivery, engagement occurs as in normal labor, and the pains are usually regular and strong. In short, there is no reason to suspect that delivery will not occur spontaneously and promptly. No progress, however, seems to occur beyond a certain point. Examination reveals that, although obliteration of the cervix is almost or entirely complete, dilatation of the external os has not occurred, and the thinned out and obliterated cervical tissue fits like a cap over the bag of waters or the fetal head.

If the condition is not recognized, the cervix is likely to become edematous from disturbance of the circulation. It may be delivered externally, still covering the fetal head (DeLee), or it may be torn off (Jentzen, cited by Porter). In some of the reported cases the uterus was ruptured.

The opening in the external os may be felt only as a tiny, pin-point depression, where the os would normally be located. Even by speculum examination it is sometimes impossible to identify the location, though usually a tiny hole is seen surrounded by a very red ring (DeLee). In the case reported by Porter, examination by speculum revealed a small stream of meconium emerging from a depression in the cervical tissue, through which, when the meconium was wiped away, a few long black hairs emerged. Such an aid to identification is, however, unique. As a rule, one must depend for diagnosis upon the digital identification of the sunken, depressed, nonresistant area which represents the external os and which is distinctive and different from the surrounding tissue, or upon its identification by speculum. Most often the direction of the depression is toward the vaginal fossa, but Katsu and Himmelsbach both call attention to the confusion which may occur when the cervix is displaced, as it was in Katsu's case, in which the external os was markedly retrodisplaced.

Cervical conglutination is usually not recognized until labor has progressed to a considerable degree. If it should be recognized early, full obliteration of the cervix should be permitted to occur before treatment

is instituted. Obliteration of the cervix is part of the normal process of labor, and attempts at manual dilatation, cervical incision, introduction of bags, and similar measures merely create complications and are to be condemned. In a few instances, if labor is permitted to continue normally, dilatation of the external os will occur spontaneously, but in most instances artificial measures must be employed because of the risk of additional dystocia as the result of edema of the cervix, or because of the possibility of traumatic amputation of the cervix or rupture of the uterus.

The simplest measure to relieve the conglutination is continued gentle, steady digital pressure upon the depression which represents the external os. As a rule, such pressure is immediately successful, the finger promptly enters the cervical canal, further dilatation occurs at once, and delivery follows immediately and sometimes almost precipitately. Traumatic manipulations should be avoided. If the finger does not enter the canal promptly by the use of a minimum degree of force, manual dilatation may sometimes be employed cautiously, but both manual and instrumental dilatation are open to the same objections, that uncontrolled tears may result from their use, and controlled crucial incisions into the cervical tissue are usually more satisfactory.

When the cervical conglutination is due to previous treatment with caustics or previous operative procedures, the location of the depression which represents the external canal may be difficult if not impossible, and the stenosis may be of such a degree and type that delivery from below might be attended with disaster. Stander (in his revision of Williams' text) has reported several cases following high amputation of the cervix in which the uterus was extirpated at cesarean section and no trace of the opening could be found, though the external os must unquestionably have existed for conception to have occurred. Under such circumstances cesarean section is probably the safest as well as the most conservative mode of delivery.

The successful outcome of the unusual case reported by Himmelsbach makes it worthy of citation. Amputation of the cervix was unwittingly done during pregnancy because the patient gave an untrue history. The presentation was breech. Engagement and effacement of the cervix was present, following abortive labor pains a week before the two-day labor ensued, which finally terminated in delivery by forceps following manual dilatation of the external os. The mother made a smooth recovery and the child survived, though resuscitation was accomplished with some difficulty.

CASE REPORTS

CASE 1.—Mrs. B., a white female, aged 28 years, para i, gravida ii, menstruated for the last time May 28, 1932, and expected delivery March 4, 1933. Her pregnancy was normal throughout and she presented no pelvic disproportion.

Her previous history was without incident, except for a perineorrhaphy and curettage of the uterus one year before the inception of the present pregnancy.

Labor began at 8 A.M. March 19, 1933. The position was L.O.A. The pains were strong and regular from the onset. Vaginal examination at the end of two and a half hours revealed effacement of the cervix to be progressing normally, al-

though no dilatation had occurred. At the end of five hours effacement was two-thirds complete, but still no dilatation could be made out, and the opening in the external os could not be located digitally. Examination by speculum revealed a pin-point opening through which the finger was readily passed. Almost as soon as the canal had been entered, two fingers' dilatation occurred. Thereafter labor progressed normally and delivery of a healthy female child, weighing 7 pounds 14 ounces, took place four hours later (nine and a half hours after the onset of labor). In this case artificial measures were employed before complete obliteration of the cervix had occurred but might not have been necessary had labor been allowed to progress without interference.

CASE 2.—Mrs. M., a white female, aged 37 years, para iii, gravida v, had menstruated for the last time May 31, 1938, and expected delivery March 6, 1939. The present pregnancy had been normal throughout, and pelvicephalography revealed normal fetopelvic relations.

Her previous history was without incident, except for two spontaneous abortions which occurred between the first and fourth full-term pregnancies. Both previous labors had terminated spontaneously in full-term, healthy children.

Labor began March 1, 1939, at 11 A.M., with strong pains at fifteen-minute intervals. The position was L.O.A. Vaginal examination eleven and one-half hours later revealed the cervix flush with the vaginal wall; the cervix was completely effaced and the impression was that the fetal head was covered by a snugly fitting cap. The external os as such could not be identified, but careful digital examination finally revealed a dimple pointing toward the vaginal fossa. When the finger was gently pressed into this area, it immediately gave way and the canal was entered without difficulty. Although no attempt at manual dilatation was made, two fingers' dilatation occurred within fifteen minutes, and complete dilatation was present at the end of an hour, following which a live, healthy male child, weighing 6 pounds, was delivered almost precipitately.

CASE 3.—Mrs. L., a white female, aged 29 years, para i, gravida ii, had menstruated for the last time September 4, 1938, and expected delivery June 11, 1939. The pregnancy had been normal throughout, and pelvicephalography revealed normal fetopelvic relations.

The patient's first pregnancy had terminated in a premature labor at six months nine years ago. She had had several superficial cauterizations of the cervix and one deep cauterization for persistent endocervicitis. Three months prior to the inception of the present pregnancy tubal insufflation had revealed patent ostia.

Labor began at 4 A.M. June 18, 1939. The position was L.O.A. The pains were strong and regular from the onset. Eight hours later examination revealed the head well down and deeply engaged. The cervix was completely obliterated and was flush with the vaginal wall; the external os could not be identified. At the end of sixteen hours pelvic examination revealed the same conditions except that there was considerable edema of the tissues which covered the fetal head and it was impossible to differentiate the cervical from the vaginal tissues. The external os could not be identified digitally or by speculum.

It was obvious that the chances of the patient securing a living child would be jeopardized by further attempts at vaginal delivery. The vaginal canal was thoroughly sprayed with 4 per cent mercurochrome solution, and low cesarean section was performed. A healthy female child, weighing 8 pounds 1 ounce, was delivered without difficulty. After the placenta had been removed, the external os was immediately identified and two fingers' dilatation was accomplished by gentle pressure, this procedure being carried out routinely at cesarean section, in order to facilitate drainage. The patient made an uneventful recovery.

SUMMARY

1. So-called conglutinatio orificii externi is an unusual, though by no means rare, cause of delayed labor.

2. The term is a misnomer, since the condition is not a true conglutination, but rather a failure of dilatation of the circular fibers around the external cervical os.

3. The clinical picture is usually typical. The opening in the cervical os cannot always be identified even by speculum examination.

4. Artificial measures are usually necessary to relieve the condition, which sometimes terminates in spontaneous delivery, but may result in prolonged dystocia, amputation of the cervix, or rupture of the uterus. Usually all that is necessary is entrance into the cervical canal by continuous gentle digital pressure against the external os. Cesarean section is occasionally required.

5. Three typical cases are reported.

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DISCUSSION

DR. RUDOLPH W. HOLMES, UNIVERSITY, VA.—The earlier authorities described two types of conglutinatio: one where there was merely a constriction (stenosis) of the external os and failure of dilatation; the other where there was an actual agglutination of the external os with absolute obliteration of the lumen. In numerous instances I have found that the former may be adequately treated by the simple rupture of the membranes. In actual agglutination, where there is no opening, some form of cutting must be employed. As cervical effacement is extremely developed in both types I have always taught that Dührssen's incisions are far preferable to cesarean section.

DR. ALFONS R. BACON, CHICAGO, ILL.—Only a few months ago we had a patient with this condition at the Municipal Tuberculosis Sanatorium.

Mrs. G. F., a primipara, began labor on a Friday afternoon and simultaneously reported leakage of liquor amnii. During Friday night, and on Saturday and Sunday she had pains of fair quality which continued until Monday morning when there was a diminution of the pains. The doctors on service made five rectal examinations, from which they reported early progress in the descent of the head to a level below the ischial spines; they also reported that they thought the cervix was completely dilated.

When I was called for vaginal examination I found that the cervix was quite thin and the external os was closed except for 1 to 2 mm. By a boring motion it was possible to get through the os, then the dilation proceeded more easily and the os was finally dilated to 5 or 6 cm. The fetal heart tones were elusive, and there was some doubt as to their existence, the patient was somewhat weakened from the long three-day labor. Dührssen's incisions were made anteriorly and posteriorly, and forceps delivery in R.O.A. position was accomplished after a deep left episiotomy. A live baby was delivered.

On the patient's first prenatal examination the cervix appeared bluish, without endocervicitis or erosion. There was a small, shallow ulcer, 3 to 4 mm. in diameter, in the anterior vaginal wall, but smears revealed no tuberculosis. This was promptly cleared up, so that I hardly think it had anything to do with the later stenosis.

DR. CARTER (closing).—With regard to manual dilatation of the cervix at the time of cesarean section, I do not attempt to put a finger through the cervix in those patients who have been in labor, but I do in all patients in whom the section is elective. The reported section was comparable to an elective one, since there was no opening in the cervix and marked edema masked the structures.

Some years ago when I served as House Surgeon in the New York Lying-in Hospital, under the late Dr. Asa B. Davis, I assisted Dr. Davis in performing a cesarean section in which the cervix was left undisturbed. In this patient there was an absence of drainage through the vagina. On the third day she developed a temperature of 105°. I made a vaginal examination and found a dimple in the external os, through which I inserted my finger. Immediately there occurred a 2 cm. dilatation with a drainage of about 2 tablespoonsful of pus. The patient then ran a normal convalescence.

The same thing occurred in one of my patients at the Baptist Hospital in New Orleans, in whom the cervix failed to dilate after cesarean section. Vaginal examination disclosed a closed cervix through which the finger was inserted, resulting in evacuation of pus. The convalescence of this patient was also normal thereafter.

THE LEUCOCYTE COUNT IN LABOR*

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THE leucocyte count is a valuable laboratory procedure. It is a definite aid to the diagnosis, prognosis, and management of many disease processes. Its adaptation to obstetrics has largely been in the field of the associated medical and surgical complications. The occurrence of a leucocytosis during labor has been known since the observations of Moleschatt[1] in 1854 and Reider[2] in 1892. Although many individuals have studied the problem, the detailed relationship of the leucocyte rise to the clinical course of labor has not been determined. The following observations are reported in order to establish a "norm" because of the clinical significance the count might have when considering complicated cases.

In 1898 Hibbard and White[3] noted that during labor the leucocyte count rose to 15,000 in primipara and 11,700 in multipara. This leucocytosis diminishes rapidly during the puerperium, with a slight elevation on the sixth day and a normal count thereafter.

In 1902 Habl[4] studied 36 cases in the last months of pregnancy, during labor, and the first week post partum. He stated that there is a slight increase in the leucocyte count in the last few days of pregnancy, followed by a marked leucocytosis at the beginning of labor. This diminishes rapidly and is normal by the end of the first week post partum. The rise is in the polymorphonuclear cells.

Carton[5] in 1903 found that a polymorphonuclear leucocytosis occurs during the last month of pregnancy, increases during labor, and is normal shortly afterwards. He found that the rise is more marked when the child is born dead or macerated, or when twins are present.

Given[6] (1906) reported the average count to be 10,500 before labor, 16,000 twenty-four hours afterwards, and 7,000 by the twelfth day.

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*Presented before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 10, 1940.

Blumenthal[7] (1907) noted that the leucocytosis was more marked after separation of the placenta than in the first stage and that the count lessened after rupture of the membranes.

In 1910 Horvath[8] stated that the peak of the leucocytosis occurred three to seven hours after delivery.

Baer[9] in 1916 studied 100 cases in which he took counts during labor and one daily thereafter for ten consecutive days. In primiparas the average count was 18,225 during labor, with 19,887 as the high point on the first post-partum day. Multiparas revealed 13,467 cells during labor, with a high of 15,062 on the first puerperal day. He found the count to be higher during obstructed labor and after rupture of the membranes. There was a gradual decrease to a normal count within seven to ten days. Jarcho,[10] Fawcett,[11] Cabot,[12] and others reached similar conclusions.

Gibson[13] in 1937 investigated the subject in 38 normal cases. She recorded findings at the end of pregnancy, the height of labor, several times during the first twenty-four hours following delivery, and daily for two weeks in the puerperium. She observed a slight rise at the end of pregnancy and a much greater rise at the end of labor, with the highest average in the "birth to two-hour" period. Counts ranging from 10,000 to 39,800 occurred during the first six hours after delivery in normal women. The same type of leucocytosis was observed in primiparas as in multiparas, but in the former it tended to be higher and to last longer.

MATERIAL

Fifty normal women were observed shortly following the onset of labor to the termination of the eight-day hospital puerperium. Twenty-five were primiparas and 25 were multiparas. Leucocyte counts were made at intervals of one to two hours shortly following the onset of labor until delivery. Counts were then made at delivery, before and after the use of oxytocics, and after the delivery of the placenta. The hemoglobin and erythrocyte counts were likewise observed in 10 patients, but as these factors remained constant regardless of the change in the leucocytes further observations were not made.

The standard technique of making a leucocyte count from blood obtained by capillary puncture of the ear or finger, as described in all texts, was followed.

Several cases of rapid labor, primary uterine inertia, secondary uterine inertia, and "obstructed" labor were also observed.

RESULTS

Twenty-one of the 50 normal patients were seen during the last weeks of pregnancy. In these patients the counts varied from 5,750 to 12,200. The average count was 8,054.

All patients were seen from one to four hours following the onset of the symptoms of labor. In the 21 patients who had been observed before labor began, the counts at this time varied from 7,600 to 12,850. In all cases there was a slight rise over the previous figure. The remainder of the 50 cases revealed similar counts, the average for this time of labor being 10,247.

As labor progressed the leucocytes gradually increased. When the cervical os became dilated 4 cm. and the average labor pain was occurring every five minutes and lasting thirty to seventy seconds, the leucocyte counts varied from 8,240 to 14,050, the average being 11,456.

When the dilatation of the cervix had increased to 8 cm., the counts varied between 10,450 and 15,620. The average count was 13,635.

At approximately the onset of the second stage of labor the average count was 15,150. At this time the leucocytes ranged from 11,120 to 23,650.

Many leucocyte counts were made before, during, and after uterine contractions during the first and second stages of labor. No appreciable difference was noted.

Rupture of the membranes in itself did not influence the count; that is, the general pattern of the leucocyte rise, as observed in all cases, continued regardless of the time of the rupture of the membranes. Cases of so-called dry labor (14 of the 50 cases) likewise did not show any difference from the normal.

Primiparas were observed every fifteen to twenty minutes during the second stage of labor. The leucocytosis continued, but in a more rapid fashion. The second stage of labor averaged two hours and eight minutes in these cases. The average count at the time of delivery was 22,250, with counts ranging from 14,760 to 27,640.

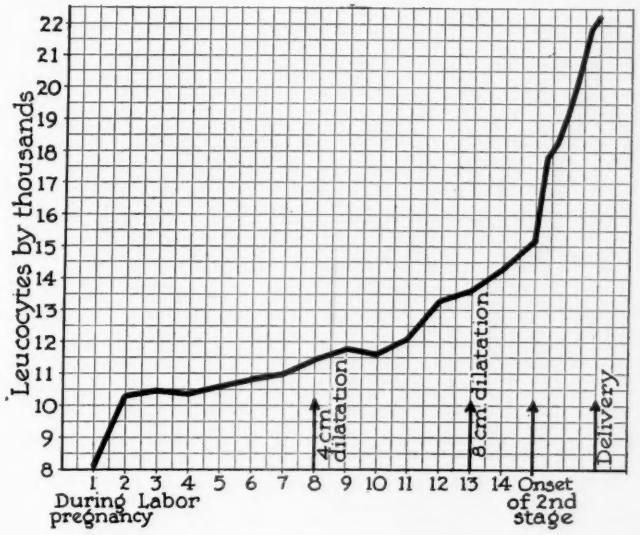

Fig. 1.—The leucocyte count in labor in primiparas.

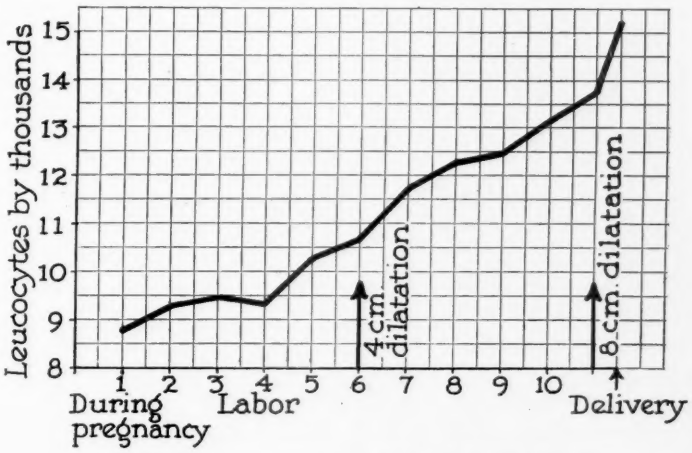

Fig. 2.—The leucocyte count in labor in multiparas.

This leucocytosis was also observed in multiparas. Counts taken near the end of pregnancy and shortly following the onset of labor revealed changes as reported above. As labor progressed, the leucocytosis continued. The counts gradually rose to 13,754 (11,980 to 14,640) when 6 to 8 cm. cervical dilatation had been reached. Because the progress was usually rapid after this stage of labor had been reached, counts were then usually taken just before, during, and after delivery. The count at the time of delivery varied from 13,250 to 16,880, the average being 15,270.

The third stage of normal labor did not affect the leucocyte count.

Following delivery, counts were taken before, during, and at various intervals after the routine use of pituitrin and ergot. No change was noted.

The majority of women were also examined during the puerperium. The leucocyte count gradually returned to normal by the seventh day. Nine patients had a count slightly higher than that noted at delivery on the first puerperal day.

Eleven cases of short labors (three to seven hours) were observed. Six were multiparas and five were primiparas. In all cases a slight increase in the leucocytes occurred shortly following the onset of labor, a gradual rise continued, and at delivery the count varied from 13,600 to 17,450, the average being 14,980.

Four cases of primary uterine inertia were studied, all in primiparas. The labors varied from fifty-four to sixty-eight hours. They were all characterized by weak, infrequent, and irregular uterine contractions during the first stage of labor. Progress was slow until a cervical dilatation of 5 to 7 cm. was reached, when the labor pains increased so that delivery followed shortly. Conservative therapeutic measures were used. The count rose slightly following the onset of labor. During the slow and prolonged first stage the count remained at this same level. After good uterine contractions occurred, the count slowly rose so that a normal pattern was then followed until delivery.

Seven cases of secondary uterine inertia were seen. In all cases the normal pattern of leucocytosis was observed until the uterine contractions became weak and ineffectual. The leucocyte count then remained at the level it had reached at this time. In two cases strong contractions recurred spontaneously, and in these the leucocytes resumed their normal march to a higher level.

Six cases of what might be termed obstructed labor were observed (persistent occiput posterior, 1; deep transverse arrest, 2; disproportion, 3). The leucocyte count followed the normal pattern, except that the rise was higher in all cases.

DISCUSSION

Before one can assume that the pattern of leucocytosis is definite for labor, the changes must be compared with the leucocyte count in the normal nonpregnant individual.

The normal count of man is stated to be from 5,000 to 10,000, with 7,500 as the average count. Supposedly there is a physiologic leucocytosis following digestion and exercise, and the count is said to vary at different times of the day. These latter facts have lately been open to question. Smith and McDowell,[14] Kenyon and Macy,[15] and Ponder[16] all noted that the white blood cell count is relatively stable throughout the day. Slight variations do occur, and an increase in the count in the afternoon is an inconsistent though fairly frequent phenomena. These changes do not appear to be due to an increase in new cells but to a redistribution of old ones. Each individual shows a slight curve of daily rhythm that is not modified by digestion, mild fatigue, moderate exercise, or menstruation.

The results reported show that a physiologic leucocytosis occurs during normal labor. It is also apparent that a definite pattern of leucocytosis is present. The onset of labor causes a slight increase in the leucocyte count. Following this, the leucocyte rise appears to be definitely related to the uterine contractions. Although the individual contraction does not influence the count, the sum total of many uterine contractions does. This is well exemplified by the course of the leucocyte count during normal labor, as compared to that in the uterine inertia series.

One cannot observe these changes without wondering what the cause may be. Previous workers have shown that the rise is only in the

polymorphonuclear elements (primarily the neutrophiles) and that the cells morphologically represent mature and aged cells and not newly developed ones. Although many theories have been advanced, the present accepted one is that the count is the result of the muscular activity of the uterus.[17] Whereas prolonged exercise does not affect the white blood cell count, severe activity can lead to a 60 to 100 per cent increase in the leucocytes.[18] Since there has been no experimental work done here to decide this question, I can only state that the work of the contracting uterine muscle appears to stimulate the mobilizing of the polymorphonuclear leucocytes into the systemic circulation.

SUMMARY AND CONCLUSIONS

1. The leucocytosis of labor follows a constant definite pattern.
2. Normal values of the leucocyte count during the course of labor are established.
3. This pattern of leucocytosis is characteristic of both primiparas and multiparas, except for the higher numerical values during the longer second stage of labor of the former.
4. Comparison of the pattern in normal and abnormal cases shows the relationship of the leucocytosis to the uterine contractions.

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30 N. Michigan Avenue

DISCUSSION

DR. JOHN I. BREWER, Chicago, Ill.—The most interesting part of this paper to me is the demonstration that with uterine inertia, or when the uterine contractions are reduced in intensity, the white blood cell count does not increase; if the uterine contractions become more severe, the white blood cell count begins to rise. On this basis it has been concluded that the rise in the leucocyte count is the result of uterine contraction.

It seems, however, that there have been some factors that have been overlooked. With the increase in intensity of uterine contractions excessive exertion occurs and that alone will increase the leucocyte count. Another factor is the pain which itself will increase the leucocyte count to as high as 20,000. There is also an increase in adrenalin output which will increase the leucocyte count presumably by contraction of the spleen with extrusion of the leucocytes into the

blood stream. Another fact is the anoxemia which probably increases the count by opening up the blood sinuses. Anesthesia and analgesia of various kinds will produce anoxemia, thereby raising the leucocyte count. There is no mention in the paper of the type of anesthesia or analgesia used.

Most reports have shown that the leucocyte counts are higher after the termination of labor. That has been thought due to the fact that hemorrhage raises the leucocyte count. Yet the work done here shows no increase in the leucocyte count after the termination of labor. With this in mind, I would like to ask how much blood loss occurred in the patients reported here.

DR. WOLFF (closing).—As to the cause of the leucocyte rise we must admit that there are many possible factors. It has been shown that excessive exertion, such as walking up and down six flights of stairs or lifting a 1,400 pound weight, until exhausted, will raise the count, while moderate exercise has no effect. Adrenalin in large doses will also raise the count.

Regarding anoxemia, I observed 2 patients with compensated rheumatic heart disease, and in both the counts were exorbitant, 35,000 leucocytes being present at delivery.

In no case was analgesia used in the first stage, but drop ether was used for the final pains. The effect of analgesia or anesthesia upon the white blood cell count in these cases was, therefore, not important.

The higher counts noted after delivery by other workers have been found within two to six hours post partum. My first post-partum count was usually taken twelve to twenty-four hours after delivery. This may account for the variation.

There was no excessive hemorrhage in any case so that I do not believe that blood loss was a factor.

SOLID TERATOMA OF THE OVARY IN THE YOUNG GIRL*

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(From the Division of Gynecology and Obstetrics, Henry Ford Hospital)

THE solid teratoma of the ovary is a highly malignant growth when found in the adolescent or preadolescent girl. It occurs infrequently. The incidence of tumor is higher in the ovary than in any other organ of the growing girl. This tumor is more likely to be benign than malignant. The cystadenomas, the fibromas, and the cystic teratomas or dermoids are benign. The malignant tumors are either carcinoma, sarcoma, or the solid or combined cystic and solid teratoma. Among the malignant tumors, the solid teratoma occurs least frequently. The gross and microscopic appearance of solid teratomas rarely suggests malignancy, but subsequent data indicate that they are more malignant than carcinomas or sarcomas occurring in ovaries of girls.

An ovarian tumor is not suspected until it produces subjective symptoms. Steel[1] states that its presence may be made known in one or more of the following ways:

(1) Increasing growth giving rise to abdominal deformity.
(2) Constitutional disturbances, as precocious sexual changes.
(3) Mechanical effects causing pressure on surrounding viscera.
(4) Complications, e.g., torsion of the pedicle.

The latter complication is present in almost a third of the cases reported. Steel found 25 cases of cysts with twisted pedicle in which

*Read before the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Ind., October 12, 1940.

appendicitis was the preoperative diagnosis. This is logical inasmuch as both twisted pedicle cysts and appendicitis are associated with nausea, vomiting, lower abdominal pain, and with or without the presence of an abdominal mass. This error in differential diagnosis is not serious. Both conditions make surgical intervention imperative.

The preoperative differentiation between a benign or malignant tumor is not probable. It is important to know what to do if a solid tumor of the ovary is encountered. Solid tumors are usually pedunculated and are well encapsulated. If any adhesions are present, they are usually of recent origin. Gross evidence of extension or metastasis is lacking. The appearance of these tumors belies their true nature. It is to emphasize this point and to offer suggestions for treatment, that 2 cases are here reported.

CASE REPORTS

CASE 1.—K. S., aged 8 years, was admitted to the Henry Ford Hospital on March 7, 1933. She had been ill three weeks with abdominal cramps associated with nausea and vomiting. The family physician had made a diagnosis of intussusception.

On admission her temperature was 99.6° F.; pulse rate, 108; respirations, 22. She appeared ill. Examination of her nose, throat, and chest was negative. A swelling in the right lower quadrant was evident. A large, firm, tender tumor mass was palpated. Rectal examination was negative. The white blood cell count was 14,700, with 84 per cent polymorphonuclear leucocytes. Appendiceal abscess was diagnosed by the surgeon and consultant. On opening the abdomen a nodular tumor, measuring 9 by 13 by 6 cm., was found, involving the right ovary. The short pedicle had become twisted. There were no adhesions about the tumor. A large amount of bloody fluid was free in the abdomen, and there was no evidence of extension or metastasis. The tumor was removed by clamping and ligating the pedicle.

The pathologic diagnosis following microscopic examination was teratoma of the ovary. The gross and microscopic description of the tumor, as given by Dr. A. O. Severance, is as follows:

Gross Pathology.—The specimen consists of large mass, originating in right ovary, measuring 9.5 by 13 by 6 cm., and nodular, the nodules being cystic. The outer surface shows gray yellow and blue mottling. The vessels on the surface are dilated. On section the cut surface presents tumor tissue with areas of yellow gray. A cyst cavity, 5 by 2 cm., is found in one pole. Hemorrhage is seen in some areas. Gray areas on closer inspection have a translucent appearance and suggest colloid in places. The cyst cavity contains brown fluid. The total mass weighs 434 Gm.

Microscopic.—Various sections taken through the ovarian tumor show similar appearance. The tumor appears to be composed of an embryonal type of tissue in which portions of all three germ layers are present. In places we see glandlike alveoli lined by columnar type of epithelium in which the epithelial cells resemble goblet cells, and the epithelium lining this gland is very much like that found in the alimentary canal or intestinal tract. Other glands are smaller and contain cells that are more columnar in shape with pinker cytoplasm and blue nuclei. Also found throughout the ovarian tumor are numerous blood vessels, large and small, lined by flattened endothelial cells. Again portions of the tumor show large areas of connective tissue. Here and there we find areas of hyaline cartilage in which the matrix is light bluish in color, the lacunae are clear, and the nuclei of the cartilage cells are dark blue in color. Another cystic area is seen in which the lining epithelium is of the cuboidal or low columnar type, and this cyst shows the epithelium projecting outward in the form of many small villous-like projections. Another area shows stratified squamous epithelium, not very thick but very much resembling that found in the skin. Also found in the sections are areas of necrosis resembling

very much caseation. There is no epithelioid cell reaction about these areas of caseation, nor are there any giant cells or other evidence to suggest tuberculosis, but some of these areas of degeneration are very extensive and are made up of light, homogeneous, pink-staining material in which we find pyknotic dead nuclei. There are other areas here in which the tissue seems to be loose, myxomatous, embryonic type of connective tissue, and in some places this contains areas of hemorrhage. A portion of the tissue present is covered by typical epithelium representing skin in which a cornified outer layer is present. There are other areas found which suggest endometrial tissue showing a stroma very much like endometrial stroma, loose in type, with cells somewhat like endometrial cells; this stroma shows the presence of glands which resemble to some extent endometrial glands. Some of the glandular elements in the sections show a few mitotic figures, but the cells are usually somewhat uniform in size and shape, and there is nothing at the present time which would suggest carcinoma developing within the tumor.

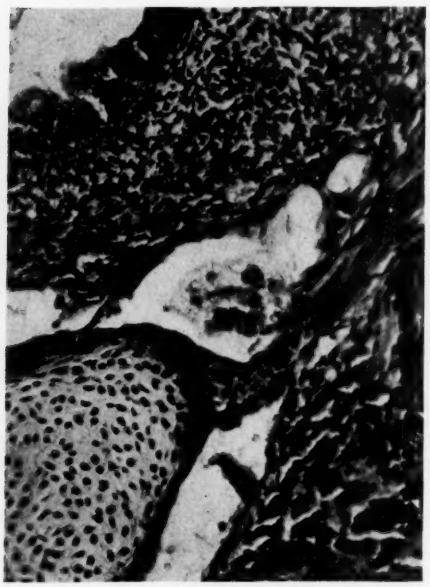

Fig. 1.

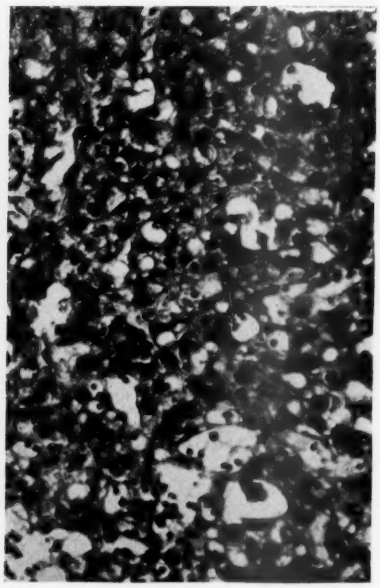

Fig. 2.

Fig. 1.—Photomicrograph, medium power, from Case 1, showing primary ovarian teratoma with areas of cartilage and epithelial lined spaces.

Fig. 2.—Photomicrograph, medium power, from Case 1, showing recurrent anaplastic tumor at time of second operation.

After remaining well for three months, the girl developed recurring attacks of lower abdominal pain. She did not see a physician until eight months later, when she was readmitted to the hospital because of these attacks. A suggestive or indefinite mass was palpable at the brim of the pelvis in the lower abdomen, and on rectal examination a definite mass could be distinguished. A second operation was delayed for three weeks because of clinical findings in the chest suggestive of tuberculosis. X-rays confirmed the diagnosis. During this time the mass rapidly filled the pelvis and lower abdomen. The abdomen was opened a second time on Dec. 2, 1933. The lower abdomen and pelvis were filled with a soft friable tumor, which was not encapsulated and which exuded from the incision. This tumor seemed to arise from the stump of the uteroovarian ligament on the right side. The left ovary was normal.

The parietal peritoneum of the anterior pelvis and abdomen was not involved. The liver and upper abdomen were normal. The mesenteric lymph glands were enlarged.

The pathologic diagnosis was recurrent teratoma.

The gross and microscopic description of the tumor, as given by Dr. J. LoCricchio, follows:

Gross Pathology.—The specimen consists of yellowish, fatty tumor tissue removed piecemeal. The largest piece is 6 cm. in its greatest diameter. The tumor has a semisolid papillomatous arrangement and a brainlike consistency. In a tube and a portion of the fundus of the uterus (uterine horn), we find tumor tissue adherent to the serosa throughout. This is a low papillomatous, grayish-red growth.

Microscopic.—Various sections from the tumor show a rather loose growth of cells with many capillaries and thin-walled vessels. These cells vary from spindle shape to polyhedral with clear cytoplasm containing numerous vacuoles, in some areas having slight resemblance to luteal cells, other areas appearing more like endothelium. The same type of cells are found throughout the tumor. There are some areas of necrosis and also hemorrhage with polymorphonuclear infiltration here and there. As to the cells themselves, they have either rounded or oval nuclei, which are hyperchromatic with red staining nucleoli and have coarse chromatin granules distributed throughout. There is slight variation in the size of the nuclei. Mitotic figures are fairly frequent. The outlines of the cells are not readily made out. In some areas, however, we observe cells which are rounded or polyhedral and have clear vacuoles in the cytoplasm; fat stains show the presence of lipoid droplets in some of these vacuoles, but comparison of the H. & E. stain with fat stain shows that not all of these vacuoles are fat, since the tumor is much more vacuolated than the fat globules and the fat stain indicate. The cytoplasm, besides being vacuolated, shows fine pink granules. Occasionally we find small trabeculae of adult connective tissue. These are thin and insignificant, the bulk of the tissue being made up of this atypical cell whose origin is somewhat doubtful.''

The girl was given a full course of deep x-ray therapy immediately. Within two weeks following the operation a definite recurrence of the tumor could be palpated in the lower abdomen. This tumor continued to grow rapidly until the child died on Jan. 23, 1934, less than one year after the first symptoms were noted.

CASE 2.—H. K., 14 years of age, was admitted to the hospital on Jan. 18, 1937, complaining of mild intermittent pain of two weeks' duration in the lower part of the abdomen. She had also noticed a swelling in the left lower portion of the abdomen. Her history was otherwise negative. The menarche was not yet established.

On admission her temperature was 102.4° F.; pulse rate, 108, respirations, 24. She was undernourished. Examination of the head, neck, and chest was negative except for some evidence of rachitis. Examination of the upper abdomen was negative. An irregular, firm, fixed tumor filled the lower half of the abdomen; this was not tender. On rectal examination the uterus was found to be displaced upward and to the right. The lower border of the tumor was palpable. At operation a tumor filling the lower abdomen and pelvis was found. This neoplasm was solid with cystic areas scattered over and through it. Small degenerated areas were bleeding. The tumor arose in the left ovary. The left infundibulopelvic ligament was edematous but not infiltrated. There was no gross evidence of extension. The tumor was excised with a wide margin. The tube was removed and the cornu of the uterus was widely resected. Her convalescence was uneventful.

The pathologic report following microscopic examination was teratoma of the ovary. The gross and microscopic description, as given by Dr. C. A. Payne, is as follows:

Gross Pathology.—The specimen consists of an irregular mass with a smooth fibrous capsule, weighing 950 Gm. The whole mass is soft and nodular. On section the parenchyma shows numerous grayish-yellow masses of tissue which represent degenerating cysts. Bits of bone are palpable throughout the tissue. Many varieties of tissue are seen. There is some hair.

Microscopic.—Section through the ovarian tumor shows a very bizarre structure containing elements from all three germ layers. Throughout the structure considerable amount of embryonal connective tissue is noted. Islands of cartilage are

also visible. In some areas miniatures of long bones are seen showing caps of cartilage with active osteogenesis and small marrow cavity. Stratified squamous epithelium, some areas of which contain sweat and sebaceous glands, are noted. Numerous irregular glandular structures, lined by low cuboidal and tall columnar

Fig. 3.

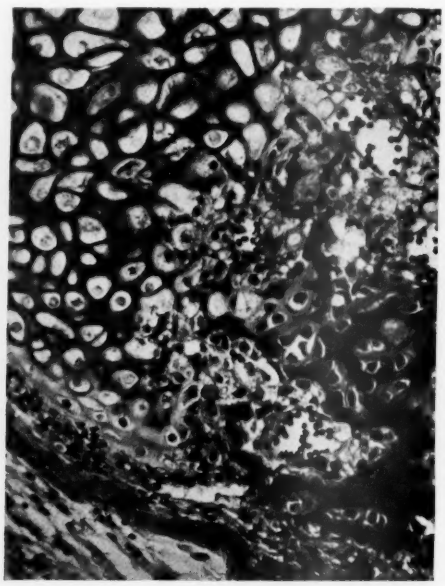

Fig. 4.

Fig. 3.—Photomicrograph, medium power, from Case 2, showing cyst lined by squamous epithelium and filled with epithelial debris. Cartilage is seen at bottom of field.

Fig. 4.—Photomicrograph, medium power, from Case 2, showing cartilage and bone from area resembling a femur.

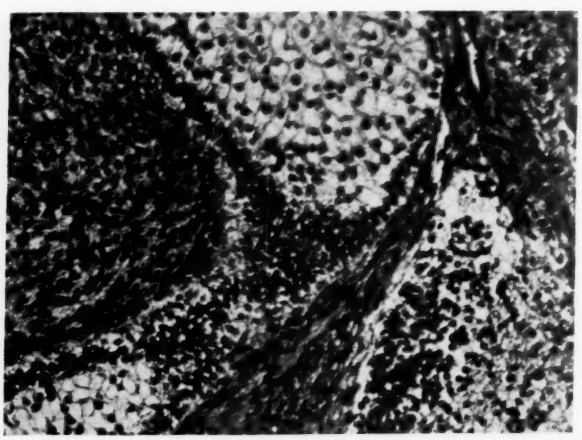

Fig. 5.—Photomicrograph, medium power, from Case 2, showing cellular poorly differentiated tissue in the recurrent tumor.

epithelium, are visible. Some of these structures resemble bronchiolar epithelium, and others resemble lung. In several areas structures resembling brain tissue and a few nerves are visible. There is no histologic evidence of malignant changes in the tumor examined.

Inasmuch as the patient was feeling well she would not return for postoperative examination. She was finally persuaded to come to the office six months later. On abdominal examination a mass was palpated above the symphysis extending one-third of the distance to the umbilicus. The circumscribed tumor seemed movable and was not tender. There were no subjective symptoms.

A second operation was advised, but the patient did not come to the hospital until a month later. At this time the upper border of the tumor, as determined by abdominal palpation had extended one-half the distance to the umbilicus. At laparotomy on Sept. 8, 1937, a circumscribed solid and cystic tumor was found to have infiltrated and invaded the omentum and fundus of the uterus. There was also involvement of the sigmoid colon as well as many implants scattered over the pelvic peritoneum. Examination of the upper part of the abdomen was grossly negative. As much of the tumor as possible was removed. The pathologic diagnosis was recurrent teratoma of the ovary. The gross and microscopic description, as given by Dr. C. A. Payne, is as follows:

Gross Pathology.—The specimen consists of an irregular, lobulated, and cystic mass, weighing 476 Gm. The tumor appears to be circumscribed, but the surface reveals many small cysts filled with a serous and mucinous fluid. On section the mass contains innumerable small cysts, composed of a light gray soft tissue which is hyperemic and shows some hemorrhagic infiltration. This tissue is supported by strands of a more fibrous nature. In a few areas there is evidence of calcification.

Microscopic.—Section through the tissue received in many areas reveals many gland spaces, some of which are lined by columnar epithelium and others are lined by squamous type of epithelium. Many glands are markedly distended and show degenerated leucocytes as well as epithelial debris. The stroma of the tumor is composed of very embryonic connective tissue, many areas of which show a myxomatous type resembling the jelly of Wharton. Many islands of embryonic cartilage are noted throughout. Masses of squamous epithelium, which show mild degree of differentiation, are also noted throughout the tumor. Some portions of the tumor are extensively necrotic and infiltrated by numerous red blood cells and polymorphonuclear leucocytes.

The patient was given a course of deep x-ray immediately, and again ten weeks later. Shortly before the second series of x-ray treatments was given, ascites appeared. No masses were palpated in the abdomen until after the second course of treatments. The abdomen then rapidly filled with recurrent tumor tissue, and the girl died in February, 1938, fourteen months after she experienced the first subjective symptoms.

DISCUSSION

In discussing the treatment of solid teratoma of the ovary, one should be familiar with its frequency and degree of malignancy. There are numerous papers in more recent literature concerning ovarian neoplasms of the young girl. These papers deal mainly with ovarian cysts, primary malignancies, or cystic teratomas. Many reports are not complete enough to allow one to judge whether the tumor is a solid or a cystic teratoma.

Witzberger and Agerty[2] collected 63 cases of ovarian neoplasms occurring in girls under 11 years of age. They reviewed the world literature between the years 1921 and 1937. Only one case cited was a solid teratoma. This case was reported in 1932 by Frank[3] and will be referred to again. An additional case was reported by Mayo and Butsch[4] in 1938.

Loeb and Levy[5] (1932) reviewed the literature on ovarian neoplasms occurring in the same age group. There was no reduplication of cases. From 1921 to 1931, they found 35 cases among which 3 can definitely be classified as solid teratoma of the ovary. One case was classified as a teratochorioepithelioma; the other 2 cases were reported from the Children's Hospital in Boston by Lanman.[6] In 1929 Lanman reviewed the admissions to the surgical service of the Children's Hospital in Boston during the preceding ten years. Of 12,260 children under 12 years of age who were admitted there were 5 with ovarian tumors. Three of these had solid teratomas; the fourth, a cystic teratoma or dermoid; and the fifth, a solid carcinoma.

Downes[7] (1921) collected 21 cases of ovarian tumor occurring since 1904. All cases were under ten years of age. None of these tumors were classified as solid teratomas.

Weil[8] reported 60 cases up to 1904 but did not classify any of them as teratomas.

Harris[9] reported a very interesting case in 1917. A subsequent report was published in 1925, ten years after the original operation. In the 1917 report he listed 21 cases of solid or cystic and solid ovarian teratomas which he found in the world literature. Twelve of these were of the solid type. In 1916 Seyforth[9] assembled 171 ovarian tumors occurring in children under 15, of which only 23 were classified as teratoma. Luftspringer[9] reported 4 cases in 1916. Probable duplication in the report prevents an accurate estimation of the incidence of these tumors. Loeb and Levy[5] (1932) estimated that there had been about 50 cases reported. This figure is as nearly correct as one can estimate today.

The survival rate reported is low. The case reported by Frank[3] survived and was well for two and one-half years after operation. May and Butsch[4] did not see their case at the time of the primary growth, but saw it after a recurrence had taken place. Presumably this case did not survive. Of the 3 cases reported by Lanman,[6] two died and one survived. Harris'[9] case was alive and well ten years later. Of the 12 solid teratomas listed by Harris, 8 are known to be dead, one was alive and well for seven years, while 3 cases were reported too soon to be certain of their survival.

In Seyforth's[9] series 20 were operated upon; 11 died within six months, and 4 had gone one year or longer without recurrence of the tumor.

In summarizing the foregoing data, we have a total of 32 cases, including the 2 in this report, in which we know the outcome. Twenty-one, or 65 per cent, of these cases are known dead, while the other 35 per cent have survived from one to ten years. Any special condition which carries a mortality rate of 65 per cent is indeed serious. The treatment needs careful consideration.

In the review of the literature it was noted that tumors were practically always pedunculated and the surgical treatment carried out was simple excision of the pedunculated tumor or adnexa on that side. The high rate of recurrence of tumor and death indicates that a more extensive surgical procedure is indicated. These tumors are usually well encapsulated. There is ordinarily a well-formed pedicle; seldom is there any more than very fine adhesions to the surrounding organs. The findings of extension or gross metastasis is rare at the time of the first operation. To all appearances when the abdomen is first opened the operator is dealing with a benign tumor, or at least one of very low malignancy. These observations, added to the fact that the patient is young, make it very difficult to proceed with radical surgery.

The pedunculated tumor recurs at the site of the original lesion. Later it spreads from this area by extension as well as metastasis. However, metastasis seems to be a late manifestation. This observation further emphasizes the need for wider excision at the time of removal of the primary growth.

The effect of roentgen-ray therapy upon this type of tumor is debatable. The only use of this form of treatment mentioned in the literawas by Frank.[3] He followed the surgical removal of the tumor in his patient with deep therapy. One and one-half years later the patient showed no evidence of recurrence of the growth.

Frank[3] compared his result with that obtained in a case seen in consultation. This patient also had a well encapsulated solid teratoma of the ovary which was

removed surgically. She was not treated with x-ray. The tumor recurred and the patient died. Frank believes that the x-ray treatments received by his patient were the deciding factor.

Both cases that I have reported received roentgen therapy. In both instances there was clinical evidence of recurrence of the tumor before the x-ray was given. In the first case, the recurrence was proved to be extensive by the laparotomy which had been performed a short time previously. The girl received one series of treatments anteriorly and posteriorly through ports covering the entire pelvis and lower abdomen. The rate of growth of the tumor was apparently not slowed and by the time the second series of treatments could have been started, the extent of the growth and the condition of the patient prevented it.

In the second case, recurrence appeared before roentgen therapy was given. The girl was given as much x-ray as she could tolerate. The first series was given immediately after the second operation; the second series ten weeks later. Ascites developed two months after the first series of x-ray. No masses were palpable in the abdomen at that time. However, shortly after the second series of treatments were given, a mass was present in the lower abdomen. The ascites continued to develop more rapidly as the lesion progressed.

We have no evidence in either case reported that the x-ray had any effect upon the tumor growth. For this reason, we question the efficacy of deep therapy in this form of growth. We agree with Frank[3] that these cases should be given x-ray in therapeutic amounts immediately after the primary operation. How effective x-ray will be in preventing a recurrence we do not know, but we do not believe it is beneficial after recurrences are present. We believe that more emphasis should be placed upon a wider excision of the original growth. This means removal of all the pelvic viscera as widely as the operator's experience allows him to dissect. The operation should then be followed by x-ray in the amount compatible with the patient's age and size. Girls with teratoma should be treated in a manner similar to adult women with carcinoma of the ovary.

SUMMARY

1. The solid teratoma when found in the ovary of the young girl is extremely malignant.

2. The literature is briefly reviewed and 2 cases of teratoma are reported.

3. The cure of this tumor depends upon complete surgical removal.

4. Our experience with the roentgen ray has not been encouraging.

5. These tumors should be treated similar to other malignant tumors occurring in the ovary.

I am greatly indebted to Dr. J. P. Pratt for his suggestions in the preparation of this manuscript, and to Dr. F. W. Hartman for the preparation and description of the photomicrographs.

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A STUDY OF 107 CASES OF UTERINE BLEEDING WITH ENDOMETRIAL BIOPSIES*

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IN UNDERTAKING this study there were a number of factors to be considered, and to leave out the rather statistical or prosaic phases of such discussion, the following are briefly some of our findings in work extending over a period of about three years.

These biopsies were obtained in the biopsy clinic of the Out-Patient Department of Gynecology and Obstetrics, Hillman Hospital, Birmingham, Alabama. They were taken without giving the patient an anesthetic. We attempted to get four specimens from each woman at weekly intervals to study the different phases of the endometrium. This study was done on patients who had uterine bleeding or menstrual irregularities, and there were a great many other patients who were seen but their attendance was not regular and they are not included in this group.

Very few of these patients came in with any suspicion of having had an abortion or suspecting retained placental tissue, but we were surprised to find 15 patients, or 14 per cent of the 107 patients, showing placental tissue which accounted for the bleeding. This is a much higher percentage than we would have believed unless the endometrial biopsies were taken to prove it.

Of the different phases of the endometrium, we found there were 95 of the 267 specimens in the proliferative stage. The pathologist found 87 in the early proliferative and 8 in the late proliferative phase. In this group 2 were found to be glandular hyperplasia and 3 to be glandular dysplasia and 2 polypoid hyperplasia.

There were one case of cystic glandular dysplasia reported and 23 of atrophic endometrium present.

This research was done, not primarily with the idea of malignancy, for where such is suspected we advise dilatation and complete curettage, but we were interested to find that there were three cases, or 2.8 per cent, of the 107 cases. This was striking, and at the same time, stimulating to us to make a more careful study of all uterine bleeders.

We noted that a great percentage of these patients who had irregular menstruation or bleeding were relieved after the 4 biopsies were taken without any further medication. So certainly, there are a large number of bleeders who have this condition present due to endocrine imbalance or endometrial disturbance and the comparatively small amount of tissue which was removed with the biopsy curette was sufficient for them to

*An abridgment of paper presented at the Twelfth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Indianapolis, Indiana, October 12, 1940.

TABLE I. ONE HUNDRED SEVEN CASES, TOTAL BIOPSIES 267

	PROLIFERATIVE PHASE, LATE AND EARLY	SECRETORY PHASE, LATE AND EARLY	HYPERPLASIA OF ENDOMETRIUM	GLANDULAR HYPERPLASIA	POLYPOID HYPERPLASIA	ENDOMETRIAL GLANDULAR DYSPLASIA	CYSTIC GLANDULAR DYSPLASIA	PLACENTAL TISSUE	MALIGNANT ADENOMA	ATROPHIC ENDOMETRIUM
Number of biopsies	95	95	28	2	2	3	1	15	3	23
Per cent of total biopsies	35.5	35.5	10.4	0.74	0.74	1.08	0.3	5.5*	1.08†	8.6

*This is the per cent of total 267 biopsies taken. (The per cent of placental tissue found in 107 cases was 14 per cent.)

†This is the per cent of total 267 biopsies taken. (The per cent of malignancies in 107 cases was 2.8 per cent.)

become regular. There are a great many who have endometrial tissue at different stages of development at the same time and to have this tissue removed in a sense regulates or starts the stages of development equally.

We felt that one of the best times to obtain these specimens, as far as giving information is concerned, is about the time menstruation is over as we would come nearer getting the basal cells for study, but we obtained them at weekly intervals regardless of the stage of the menstrual cycle.

The average age of this number of patients was thirty-eight years, the youngest fourteen and the oldest sixty-nine. One of the older patients who had continued bleeding after the biopsies were made with report of endometrial hyperplasia, was admitted to the hospital and a laparotomy was done, finding the uterus was rather normal in size, and ovaries very slightly enlarged, but with history of bleeding, hysterectomy was done, also bilateral oophorectomy. On microscopic examination patient was found with granulosa cell tumor of the ovary.

The average number of biopsies in this series of study was 2.4 per patient with the total ranging from 1 to 24 biopsies to each patient.

In the past we have been prone to overlook the ovaries of uterine bleeders too frequently. Cystic ovaries or other pathology, such as granulosa cell tumor cases of the ovary, is often the controlling factor, in fact the whole cause.

With the study being made on the endometrial tissue if we could do a laparotomy at the same time with resection of these presumably simple cysts in the ovary, as well as some of the solid tumors of the ovary, this would prove of very great value.

In consideration of the race as to white and colored, there were 75 whites and 32 colored individuals in this series, which is interesting, for in our general gynecologic clinic we have a rather high percentage of colored patients and a great many of them have fibroids, so you see the incidence of bleeding with fibroid is less than the bleeding which occurs with the endocrine disturbances.

In this group of women there were 70 gravidas and 37 nongravidas.

One point of interest was the number who had positive Wassermann reactions: there were only 7.1 per cent of these including both colored and white. It is not our opinion that the positive Wassermann reactions had a very great deal of bearing as a causative factor in the bleeding of these patients. Of course, there might have been some who had constitutional upsets that would have caused bleeding such as you find with other types of anemia.

All of these specimens were obtained by the use of the suction curette; we preferred this to the ordinary bite curette, for we are able to obtain more tissue and go over a larger endometrial area than we probably would with an ordinary bite curette.

It has been instructive to observe some of these cases over a period of more than three years which has enabled us to keep up with their menstrual history and have noticed that without treatment, other than the biopsy, they are corrected and would go for a number of months without any other menstrual disturbance.

Some of these cases have shown decided changes in the amount of endometrial tissue after the administration of one of the gonadotropic substances. So, certainly, there is a place for their use in these bleeding cases if a proper diagnosis has been reached. But it is quite essential to study the endometrial tissue before administering the gonadotropes.

There has been a marked decrease in the number of bleeding patients admitted to the Hillman Hospital for dilatation and curettage since this biopsy clinic has been going; for the majority of them we are able to diagnose and give such treatment in the clinic so they do not have to be admitted. It is well to have some means of a clearing house for these patients before admission. Naturally, we have a large number in a charitable institution, such as this. The daily average for the hospital for 1939 was 337 patients with a bed capacity of 450.

Of the endometrial biopsies there were 23 specimens which showed atrophic endometrii, which indicates that a number bleed even though the endometrium is of the atrophic type.

The hope for correct treatment lies in the accurate diagnoses, and much can be done in the study of uterine bleeders of the nonmalignant type. When we are able to do assays more generally to determine as to whether there is an excess or deficient amount of estrogenic or gonadotropic substance in the system, we shall be able to know more how to prescribe for our patients' needs.

While we are going through this process of investigation, we should be less prone to radical surgery unless there is pathology such as malignancy, fibroids or other trouble that cannot be corrected with medical treatment. If we will properly discuss the prognosis with these patients, letting them know that these are tedious conditions to deal with and require time, not only for several months but a year or so, they will be more cooperative and help us a great deal.

I feel that in all cases of uterine bleeding basal metabolism tests should be done, because there are many women who have thyroid,

either hypo or hyper conditions, in whom, if properly diagnosed and treated, the bleeding can be corrected.

The study of these bleeders as to decades is shown in Table II.

The ages of the patients with malignant conditions were 26, 51, and 59 years. Malignancy is no respector of persons or age, so we should not let a patient who is bleeding go without a thorough examination, regardless of whether she is of the younger or older group.

TABLE II

1	10-20 years	7
2	20-30 years	32
3	30-40 years	39
4	40-50 years	17
5	50-60 years	10
6	60-70 years	2

We are very much gratified in the findings of these patients whose condition was in the earlier stages, and if we are more diligent in doing biopsies early, we will find more of these malignancies at a stage in which something can be done for them.

SUMMARY AND CONCLUSIONS

1. An examination of the endometrial tissue is of great importance, as it closely reflects the functional activity of the ovaries in most cases of abnormal bleeding.

2. A diagnosis of irregular menstruation as a pathologic condition should always be made with a great deal of hesitancy, owing to the variation of the cycle of normal individuals.

3. The menstrual cycle is definitely under the control of the endocrine system. The most fundamental glands bearing relation to this function are the anterior hypophysis, the ovaries, and the thyroid.

4. In this study of 107 cases over a period of three years, the average age was 38, the youngest 14 and the oldest 69.

5. The average number of biopsies was 2.4, ranging from 1 to 24 to each patient.

6. The number of positive Wassermann reactions was 7.1 per cent, including both whites and colored. In our opinion this was no factor in the cause of bleeding.

7. There were 75 white and 32 colored patients.

8. The incidence of malignancies found in this group unsuspected was 3, or 2.8 per cent, of the 107 cases, ages of patients being 26, 51, and 59 years.

9. There were in this group 15, or 14 per cent, who had retained placental tissue.

I wish to thank Dr. Harold Imerman and Dr. Reuben Harris, Residents on Gynecology and Obstetrics, Hillman Hospital, also Dr. J. W. MacQueen, Director of the Hospital, Dr. George S. Graham and Dr. L. C. Posey from the Department of Pathology, and other members of the Staff who referred cases for study.

THE THERAPEUTIC VALUE OF TUBAL PATENCY TESTS IN STERILITY AND INFERTILITY*

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THE determination of tubal patency is accomplished by two well-established methods: the insufflation of gas and the injection of iodized oil. Transuterine tubal inflation was first performed by Rubin in 1920 as a means of testing tubal patency, and the use of iodized oil in visualizing the Fallopian tubes was first reported by Heuser in 1924, although previously (1914) Cary attempted hysterosalpingography using collargol as the radiopaque substance. From the use of these methods as exclusively diagnostic procedures, their therapeutic value soon became evident.

In 1932 Rubin collected 764 cases of pregnancy from the literature, all of which were attributed to the effects of insufflation. In his own series, 17.5 per cent of those patients who were insufflated for sterility became gravid. His results were particularly noteworthy in 570 cases in which were demonstrated some organic obstruction to tubal patency, such as adhesions or strictures. Of this group, 123, or 21.6 per cent, became pregnant. Rubin concludes that tubal insufflation has a definite therapeutic value in sterility. This is attested by the actual improvement in tubal patency and function during repeated insufflations and the pregnancy which follows shortly afterward. He condemns the use of lipiodol as dangerous, and limits its use to those cases where insufflation reveals the presence of closed tubes or high-grade obstructions. However, in 9 of his cases where gas insufflation revealed nonpatency, lipiodol succeeded in passing the fimbriated end. On the other hand, patency was demonstrated to gas but not to oil in 8 patients. The literature is replete with many other reports substantiating the therapeutic value of insufflation. Series of case studies have been reported by King (11.6 per cent), Chatillon (15.2 per cent), Bonnet (18.4 per cent), Violet (6 cases), and Mintz. The latter found that diathermy combined with insufflation exerted a curative effect upon some chronically diseased tubes, leading to restoration of patency and subsequent pregnancy. Of 44 cases, patency was re-established in 25, and in the latter 9 pregnancies occurred. Stein and Leventhal, in analyzing 300 sterile couples, reported 26.3 per cent pregnancies out of 57 infertile couples treated by pertubation alone, the pregnancies occurring immediately to more than one year after the test.

The value of oil instillation as a therapeutic measure and its superiority to gas insufflation is supported by many authors, especially the French, who were the first to recognize the therapeutic effect on sterility of iodized oil used in hysterosalpingography.

In 1936 Francillon-Lobre and Dalsace reviewed the results obtained with hysterosalpingography in 585 cases of sterility collected over ten years. Of this number, 434 showed patency to one or both tubes, and 89, or 20.5 per cent, conceived. In 6 cases pregnancy supervened even though the tubes were impermeable to oil. The

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authors conclude that if a sterile woman has one tube patent, she has one chance in five to become pregnant after hysterosalpingography. Robins and Shapira did uterotubography in 330 patients with sterility. In 133 of this group in whom one or both tubes were found or caused to be patent, 32 per cent became pregnant. Other authors who have reported cures of sterility following oil instillation are White (32.5 per cent), Beclere and Francois (18 per cent), Volk (25 per cent), Wilson (26.3 per cent), Brault and Tizon (26 per cent), and Schultze (25 per cent). Most of these declare that the risks associated with lipiodol are not greater than with carbon dioxide, and the therapeutic results are better with the former.

The method we used in the investigation of sterility is as follows: We thoroughly investigated the patient complaining of sterility for extrapelvic factors, such as foci of infection, chronic debilitating diseases, and glandular dyscrasias. If vestiges of recent pelvic inflammatory disease are not found and if the cervix displays no evidence of infection, the patient is instructed to report to the office on a date approximating the time of ovulation (figured in accordance with the cycle). She is also instructed to have normal coitus just before the office appointment. Material for a Huhner postcoital sperm test is obtained by aspirating some cervical mucus with an "asepto" syringe. The cervical mucus just within the external os is then removed following liquefaction with caroid powder; and after drying the external os cervix and vaginal vault with cotton pledgets, a 2 per cent aqueous solution of mercurochrome is applied topically. The direction of the cervical canal is determined with a sterile uterine sound, and the Stein self-retaining cannula is inserted. Carbon dioxide is insufflated transuterinely under low pressure, using the Rubin apparatus with manometric control. The tubes are declared impermeable to gas if no patency is demonstrated after three attempts up to 200 mm. Hg pressure. *We have noticed no ill effects or infections which could be attributed to the preliminary intercourse, and feel that this routine is probably a factor in the high percentage of pregnancies which followed insufflation in our series of cases.* If the tubes are not patent to gas, the patient is instructed to report for lipiodol instillation within the following day or two. This examination is carried out in the hospital x-ray department and serial roentgenograms are taken, including a twenty-four- or forty-eight-hour film if no patency is shown initially. If lipiodol instillation fails to reveal any tubal patency, it is repeated in two months. In cases of tubal closure, the x-ray demonstrates the site of obstruction and is invaluable in selecting cases suitable for surgical intervention. In a few cases in our series where tubal obstruction was encountered, one ampoule of surgical pituitrin was administered hypodermically with the instrument in situ in an attempt to overcome adhesive closure by increasing intracavitary pressure. In some instances the presence of intrapelvic pathology was questionable and pneumoroentgenography was performed using the combined method of Stein and Arens. In these cases pneumoperitoneum was always attempted by the transuterine route first and lipiodol was instilled unless contraindicated.

ANALYSIS OF CASES

Between January 1, 1930, and January 1, 1940 (ten years) 285 patients complaining of sterility or infertility were thoroughly investigated in our private practice. A critical analysis of these cases was undertaken in order to evaluate the importance of tubal insufflation and oil instillation as therapeutic measures. In the entire group of 285 patients, considering all etiologic factors and all types of treatment, conception occurred in 88, or 31 per cent. Not every patient who consulted us for sterility had a pateney test performed. When an obvious cause was discovered at the initial examination, it was treated first. Thus, chronic endocervicitis with erosion or eversion was encountered in many instances, and its eradication by cautery was followed not infrequently by conception.

The tubal patency test, using carbon dioxide or lipiodol or both, was performed on 165 patients. Eliminating those patients from this group in which male deficiencies and definite glandular dyscrasias were factors, there remained 133 patients in whom the importance of tubal insufflation or oil instillation as a therapeutic measure could be evaluated. Of these 133 patients, 114, or 85.7 per cent, demonstrated patency of one or both tubes to gas or oil, and of the latter, 51, or 45 per cent, became pregnant. Nineteen, or 14.3 per cent, demonstrated no patency, and only 3 of these, or 15.8 per cent, became pregnant. *Thus 54, or 40.8 per cent, of the entire group of 133 patients became gravid.* The average duration of marriage in the successful group was 3.8 years as compared with 5.2 years in the unsuccessful group, and the duration of sterility in the two groups was 1.7 years and 3.0 years, respectively (Table I).

TABLE I. ANALYSIS OF 133 PATIENTS IN WHOM THE THERAPEUTIC VALUE OF THE PATENCY TEST COULD BE ESTIMATED

	NO.	AGE (AVG.)	MARRIED (AVG.)	DURATION STERILITY	PATENCY +	PATENCY -
Pregnancy	54 (40.6%)	27.7 yr.	3.8 yr.	1.7 yr.	51	3
No pregnancy	79 (59.4%)	31.2 yr.	5.2 yr.	3.0 yr.	63	16
Total	133				114 (85.7%)	19 (14.3%)

In 38, or 28.5 per cent, of the patients pregnancy occurred within two months of the patency test. Some other form of therapy which might have been responsible for a cure of sterility was employed on 10 patients in this group, 7 having had cervical cauterization for erosion and endocervicitis, and 3 thyroid therapy, even though the basal metabolic rates were within normal range. The cauterizations were done six months or more before the patency test. Generally accepted criteria by which the responsibility of insufflation may be estimated include pregnancy within two months and the absence of other therapeutic measures. Since 28 patients in our series met these requirements then *21.5 per cent of the patients on whom the tubal patency test was performed became pregnant, the pregnancy being attributed directly to the procedure.* Further support for the therapeutic value of the patency test in these cases is added by the fact that the average duration of sterility was 1.7 years and the average duration of marriage for the group was 3.8 years. The longest duration of marriage was thirteen years and the shortest was one year. The longest duration of sterility was nine years and the shortest was six months. Of the 28 successful patients who became pregnant within two months, and on whom no other form of therapy was used, 14, or 50 per cent, conceived immediately without an ensuing menstruation; 23, or 82 per cent, conceived within one month of the patency test. There were 6 patients in the successful group, or 15.8 per cent, who had some associated pathologic condition (Table II). One had fibroids, 2 had a third degree retroversion of the uterus, 2 had a history of previous febrile abortion, and 1 had a previous pelvic laparotomy. In one patient who had a previous septic abortion, no patency was demonstrated with either gas or oil, and in the other, gas did not pass through, but the oil entered the peritoneal cavity after twenty-four hours. In the 2 patients who exhibited third degree retroversion, the tubes were impervious to gas and demonstrated patency to oil only after twenty-four hours. The incidence in the group that failed was 44.3 per cent. Table III demonstrates the relationship of the patency test to pregnancy and associated pathology in the 133 cases. Of the 63 unsuccessful cases with positive patency, 27, or 42.5 per cent, had associated pathology. Thus the factor of associated pathologic conditions is an important one in influencing the therapeutic effect of insufflation and oil instillation. The associated pathologic conditions, encountered in the order of their frequency, included previous pelvic laparotomy, fibroids, previous febrile abortion,

TABLE II. ANALYSIS OF PREGNANCIES WITHIN 2 MONTHS OF PATENCY TEST (38 PATIENTS)

	NO.	OTHER THERAPY*		NET RESULTS 133 CASES		AGE (AVG.)	MARRIED (AVG.)	STERILITY			ASSOCIATED PATHOLOGY
		CAUTERY	THYROID	NO.	%			DURATION	PRIMARY	SECONDARY	
Pregnancy stat.	17	3	0	14	10.5	29 yr.	4.0 yr.	1.6 yr.	12	5	4
Pregnancy in 1 month	12	2	1	9	17.3	28 yr.	4.0 yr.	1.7 yr.	11	1	1
Pregnancy in 2 months	9	2	2	5	---	26 yr.	3.3 yr.	1.8 yr.	7	2	1
Total	38	10		28	21.5	27.7	3.8 yr.	1.7 yr.	30	8	6(15.8%)

*The average time by which cautery preceded insufflation in the 7 patients was 6 months.

The B.M.R. rate was normal in the 3 patients who received thyroid therapy.

TABLE III

ASSOCIATED PATHOLOGY IN PATIENTS TREATED BY PERTUBATION (133 CASES)*

PATENCY CO_2 AND LIPIODOL	SUCCESSFUL (PREGNANCY)		FAILURE (NO PREGNANCY)	
	TOTAL NO.	ASSOCIATED PATHOLOGY	TOTAL NO.	ASSOCIATED PATHOLOGY
CO_2 +	22	5 or 22.7%	30	12 or 40.0%
CO_2 + Oil +	15	2 or 13.3%	20	10 or 50.0%
CO_2 + Oil -	1	0	5	3 or 60.0%
CO_2 - Oil +	13	7 or 53.9%	7	2 or 28.7%
	3	3 or 100 %	7	6 or 85.7%
CO_2 -	0	0	9	2 or 22.2%
Oil +	0	0	1	0
Total	54	17 or 31.4%	79	35 or 44.3%
Patency +	51	14 or 27.5%	63	27 or 42.5%
Patency -	3	3 or 100 %	16	8 or 50%

*In order of frequency: previous pelvic surgery, fibroids, previous febrile abortion, adnexitis, retroversion, ovarian cyst, previous ectopic pregnancy, previous puerperal sepsis.

adnexitis, retroversion, ovarian cyst, previous ectopic pregnancy, and previous puerperal sepsis. Even without any obvious palpatory findings, previous pelvic surgery and previous septic abortion were included, because with these conditions there may occur functional changes in the Fallopian tubes and indiscernible adhesions. It is to be noted that the incidence of associated pathology is greater in the series of failures than in the successes with the exception of 2 groups in the successful series; namely, where the tubes were nonpatent to gas but patent to oil, and where nonpatency was demonstrated with both agents. This demonstrates the value of the test in overcoming tubal obstruction.

A total of 42 per cent of all the patients in whom the tubes were patent to gas alone or gas plus oil became pregnant (37 of 87). A positive illustration of the therapeutic value of insufflation alone is demonstrated by one patient in our series, who conceived immediately after the Huhner and patency tests on two occasions three years apart. Preceding each test, there was a one-year period of infertility. In six instances where the tubes were patent to gas but nonpatent to oil, pregnancy occurred only once. Thirteen of 20 patients who demonstrated no patency to gas and who later evidenced patency to lipiodol became gravid; whereas none of 9 patients who were negative to gas and on whom there was no follow-up with oil conceived. This observation may be interpreted as evidence for the superiority of lipiodol instillation over insufflation in the cure of sterility. The high incidence

of associated pathology in the successes in this group adds further weight to the role of lipiodol in overcoming tubal dysfunction and obstruction. This was further illustrated in 3 of our successful cases where the tubes showed no patency to either gas or oil. One patient had a previous febrile abortion, and examination revealed a third-degree retroversion. Patency to gas failed on two occasions. Two oil instillations done four months apart failed to show "spill" after forty-eight hours. After the second instillation pregnancy occurred without an ensuing menstruation.

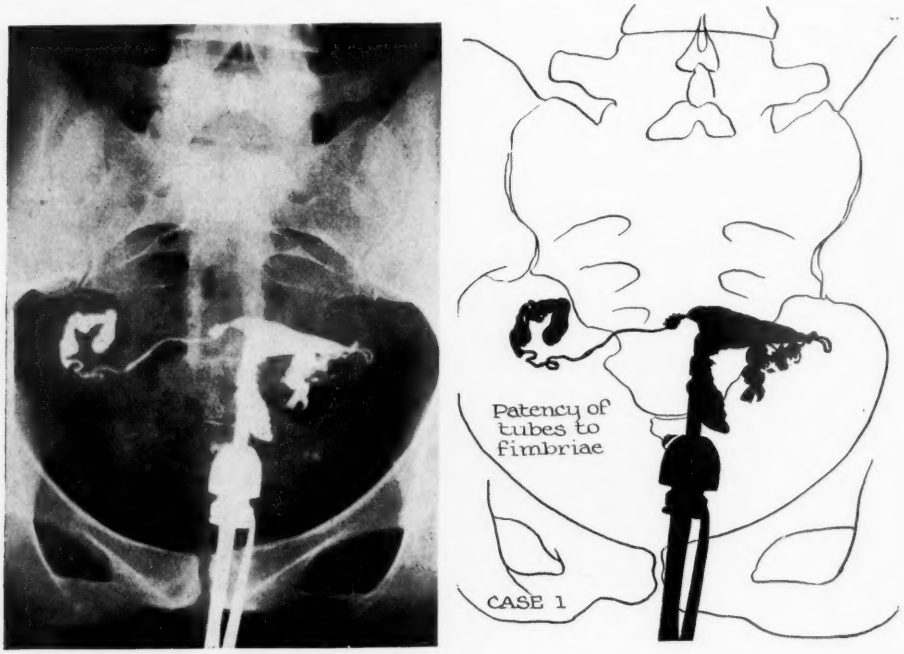

Fig. 1.—(Case 1.) Illustrating closure of tubes at the fimbriae. Previous gas insufflation negative.

The second case, with a third-degree retroversion, failed to show patency to oil on two occasions, and pregnancy followed within three months of the last test; and the third, after three negative results with oil, conceived over one year later. These cases demonstrate as prima facie evidence the curative role of lipiodol instillation in the treatment of sterility.

Other illustrative case reports include the following:

ILLUSTRATIVE CASES

One patient, C. H., who was married nine years and was sterile seven years had three previous positive patencies performed with carbon dioxide in the past six years. Instillation of lipiodol was followed within three months by pregnancy.

Mrs. T. B., was married thirteen years and sterile for nine years. The tubes were nonpatent to gas in three attempts to 200 mm. Hg pressure. Oil instillation the following day revealed the tubes patent to the fimbriated ends, and "spill" was noted after twenty-four hours. Pregnancy occurred without an ensuing menstruation.

Pregnancy occurred within two months in Mrs. J. P. who showed the same findings as Mrs. T. B., after a period of sterility of eight years.

Mrs. L. P., married 3 years, complained of sterility for one and one-half years. The Huhner and patency tests showed normal sperm, but no patency to gas. The following day, insufflation was again attempted and was found negative. Instillation

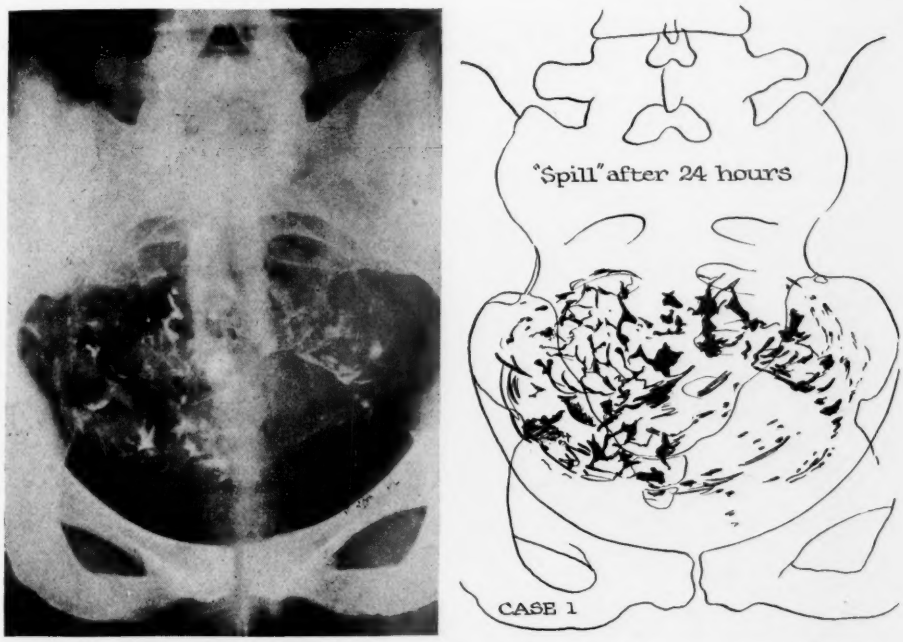

Fig. 2.—(Case 1.) Demonstrating final patency after twenty-four hours as shown by intraperitoneal "spill."

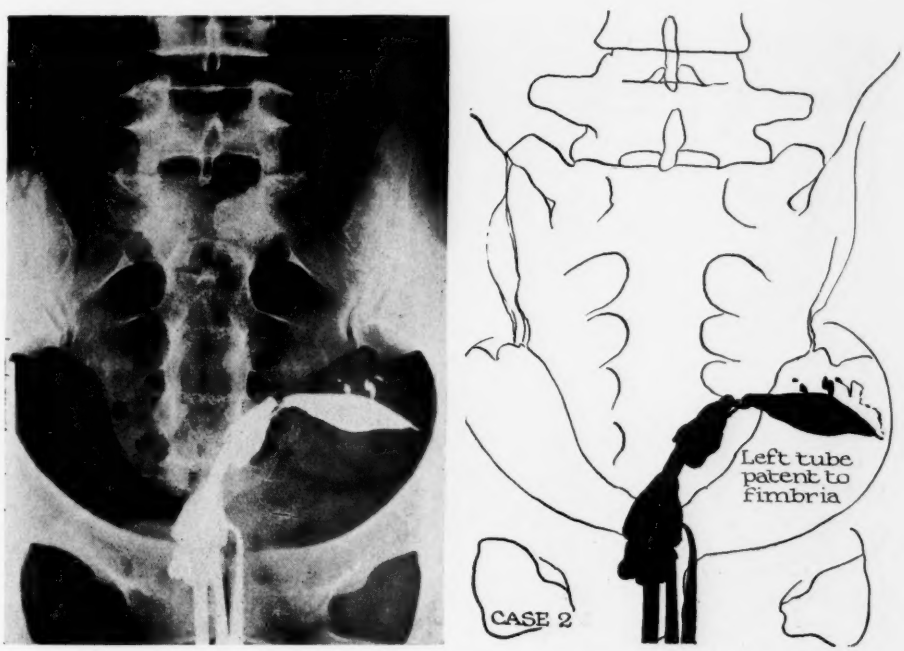

Fig. 3.—(Case 2.) Right cornual closure and left fimbrial closure to lipiodol. No patency demonstrated to gas. Acute suppurative appendicitis seven years previously.

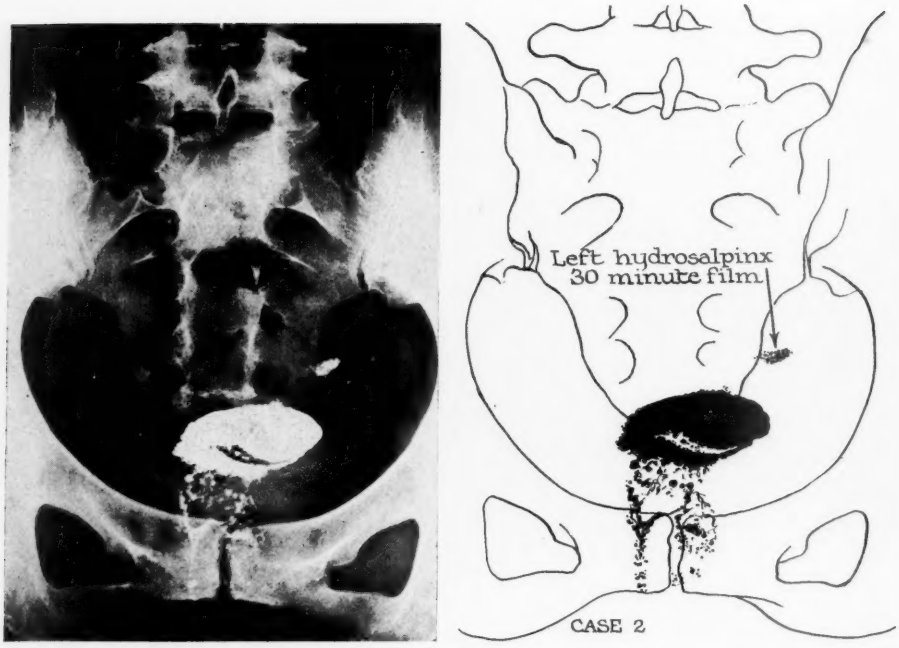

Fig. 4.—(Case 2.) Left hydrosalpinx thirty minutes after oil instillation. No evidence of "spill."

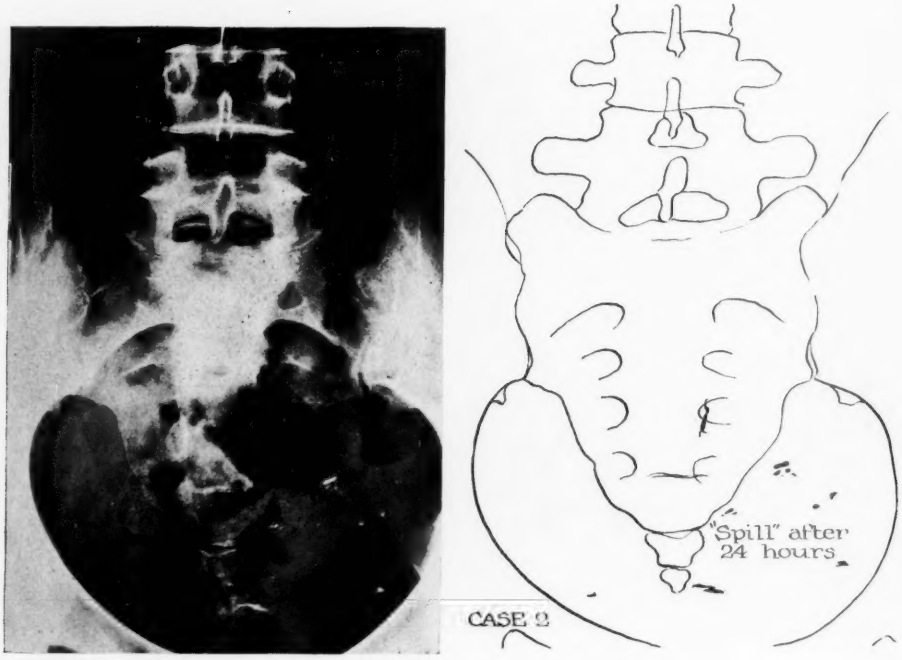

Fig. 5.—(Case 2.) Patency of left tube demonstrated by intraperitoneal "spill."

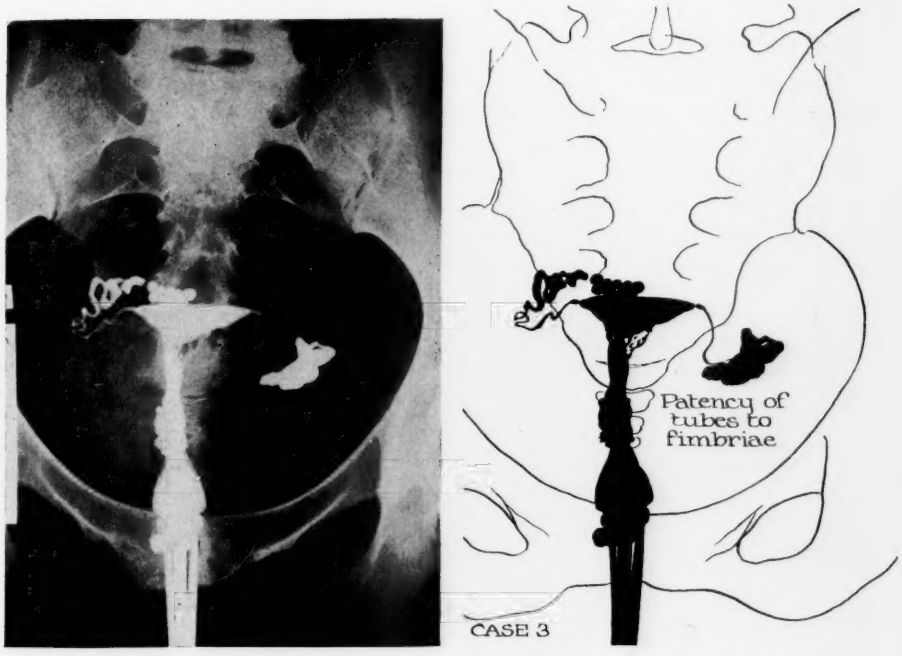

Fig. 6.—(Case 3.) Bilateral fimbrial closure with hydrosalpinx.

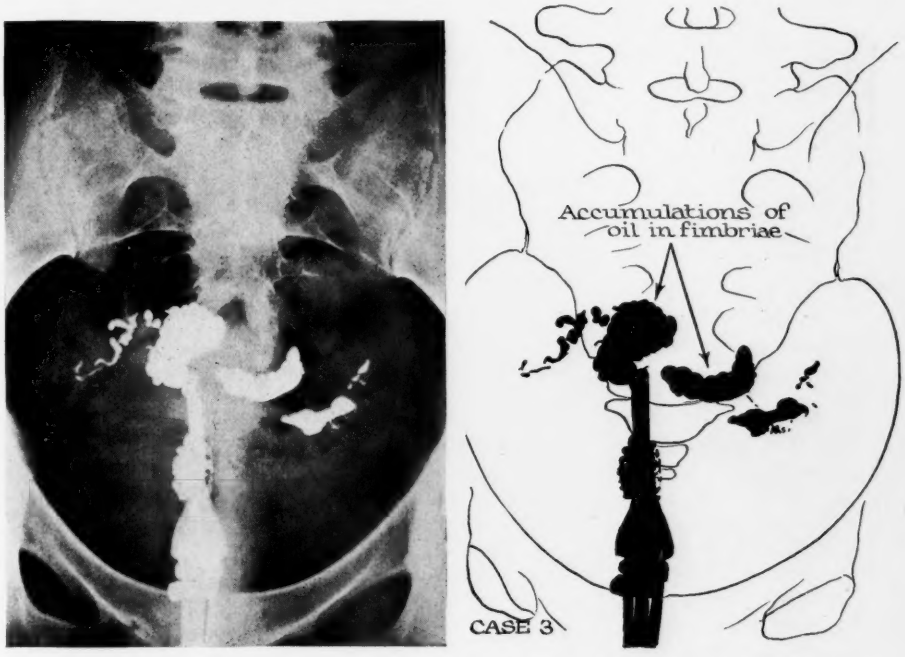

Fig. 7.—(Case 3.) Film taken thirty minutes after film shown in Fig. 6 and demonstrating a greater accumulation of oil in the dilated fimbriae. No true evidence of complete patency.

of oil disclosed patency to the fimbriated ends, and twenty-four hours later "spill" was noted (Figs. 1 and 2). There were 13 such patients in whom pregnancy occurred within two months of the test.

Mrs. A. G., married two years and sterile one year, had an appendectomy for acute suppurative appendicitis seven years previously. On June 13, 1939, insufflation following coitus revealed no patency with three attempts to 200 mm. Hg pressure. On July 8 lipiodol instillation showed the right tube closed at the cornua and the left tube open to the fimbria (Fig. 3). A thirty-minute film showed a left hydrosalpinx (Fig. 4); a slight "spill" was demonstrated on the twenty-four-hour film (Fig. 5). The patient became pregnant two months later. The etiologic factor in tubal closure in this case was probably acute appendicitis.

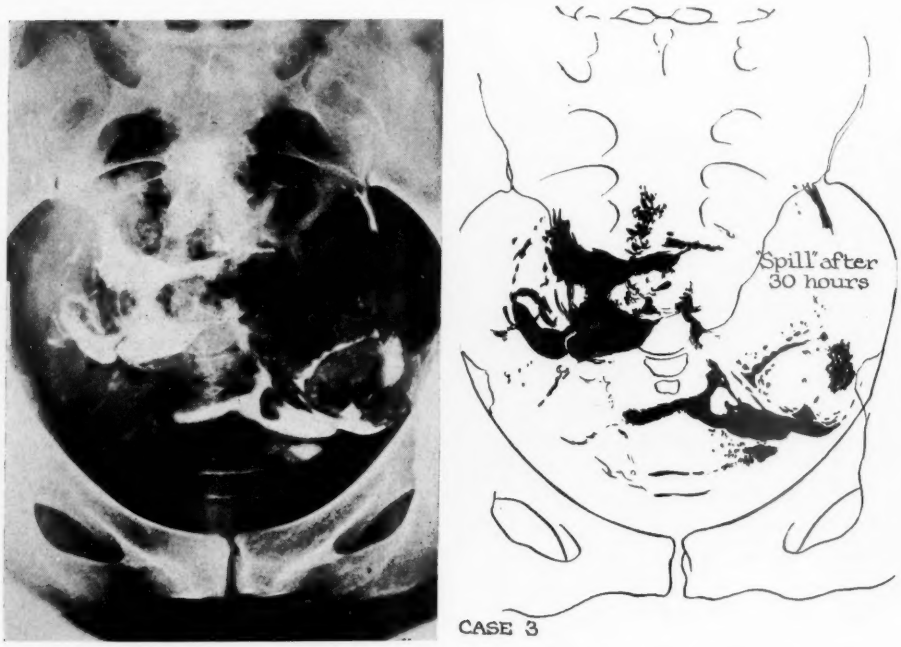

Fig. 8.—(Case 3.) Illustrating the final passage of oil into the peritoneal cavity (thirty-hour film).

Mrs. M. P. was married one year and complained of sterility of six months' duration. Bimanual examination revealed a third-degree retroversion and adnexal tenderness. On Oct. 31, 1939, the tubes were negative to gas insufflation. On November 2 lipiodol instillation revealed a bilateral hydrosalpinx without evidence of "spill" (Figs. 6 and 7). A thirty-hour film showed marked bilateral "spill" (Fig. 8). Nine days after this procedure, the patient developed severe pain in the lower abdomen and a fever. Bimanual examination revealed a left adnexal mass, which was tender, fixed, and as large as the uterus. In spite of this, the patient conceived without an ensuing menstruation, and at eight weeks, the inflammatory mass had disappeared. At the examination six weeks after a normal confinement, the pelvic status was normal. This case illustrates the concomitant occurrence of pregnancy with the lighting up of an old pelvic inflammatory process, and demonstrates the value of oil in overcoming tubal obstruction.

DISCUSSION

The effect produced by insufflation which makes possible ensuing pregnancy may be explained almost entirely on a mechanical basis. The

restoration of partial or complete patency in diseased tubes has been repeatedly demonstrated. It is not uncommon to encounter cases of tubal stenosis in which successive insufflations, either immediately or after an interval, show definite reduction in the pressure level at which patency becomes manifest. Obstructions such as inspissated mucus within the tubal lumen may be expelled, a tortuous tube may be straightened, and adhesions may be broken down. All these actions have been observed at laparotomy during which transuterine insufflation was performed. The peristaltic muscular action of the tube is stimulated by insufflation in a manner similar to the bowel stimulation brought about by intralumenal distention. This increased muscular activity enhances fertilization. Other factors which must be taken into consideration are the dislodgment of the cervical mucous plug by the cannula; ovulation induced by the mechanical stimulation of the cervix; and, if done, after coitus, the upward thrust of sperm into the uterine secretions toward the uterotubal ostia.

The value of pertubation in curing sterility is especially demonstrated in patients where some associated pathologic process causes interference with tubal function. In Rubin's series of cases (1932) partial obstruction or nonpatency was noted in 60 per cent of those who had had appendicitis, in 58 per cent of those with fibroids, in 82 per cent of those with a residual tube following ectopic pregnancy, and in 65 per cent of those with retroversion. As previously noted (Rubin), 21.6 per cent of a group of 570 patients with sterility who had some organic interference with tubal patency, became pregnant. Associated pathologic conditions which may have produced tubal obstruction in our series have been analyzed and presented in Table III. It is interesting to note that there were 2 patients in our series with third-degree retroversion in which no patency was demonstrated to gas or oil, but who nevertheless conceived, one without an ensuing menstruation and one within three months of the test. Two other successful patients with third-degree retroversion showed no patency to gas, and lipiodol "spill" was noted only after twenty-four hours. The value of oil in eventually overcoming tubal obstruction in these cases cannot be overlooked. Retroversion of the uterus is not uncommonly associated with sterility. Bonney has suggested that in some instances of retroversion, kinking of the tubes occurs, which may later become permanent due to organic shrinkage of the mesosalpinx. Examples of pregnancy following the patency test in patients with previous pelvic operations, previous appendicitis, and previous induced abortions were included in our series.

The relative value of gas insufflation and oil instillation has been the subject of much controversy. Rubin favors insufflation and uses lipiodol only occasionally. In 3,600 insufflations he found no serious complications, whereas in 132 cases with lipiodol instillation he noted 6 patients with mild peritoneal reaction and 3 who developed pelvic abscesses requiring operative intervention. King favors gas insufflation which he used in 300 reported cases without mishap and reserves the use of lipiodol for cases where extra information is needed in closed tubes.

Rabbiner condemns the routine use of lipiodol and quotes several case reports by others showing the dangers encountered. On the other hand, many competent observers favor lipiodol over gas insufflation in determining tubal patency. Robins and Shapira studied the value of hysterosalpingography in 1,000 cases. They state that it gives much more information than insufflation and is attended with no harm in properly selected cases. They noted many instances where oil showed the tubes to be patent where gas could not pass through them. On repeating the insufflation subsequently they met with failure. They proved that oil has a therapeutic value in sterility by noting in autopsy specimens that under ordinary pressures, oil released adhesions and straightened out kinks of the tube. In 1,000 cases the only morbidity attributed to the instillation was the rupture of a large hydrosalpinx. The authors conclude that lipiodol does not harm the normal membrane of the uterus and tubes and does not set up peritoneal irritation. This view is shared by many others. White states that lipiodol seems to be of greater use than gas in the treatment of sterility, because the heavier oil exerts a more constant and prolonged hydrostatic pressure. Stein encountered no pelvic abscess nor any demonstrable morbidity in over 500 cases of lipiodol instillation. Reis and DeCosta did histologic studies on 30 Fallopian tubes removed at laparotomy which had been injected with lipiodol at varying periods before operation. In no instance could they demonstrate foreign body reaction.

In our series the value of lipiodol, after failure of insufflation to demonstrate patency, has been repeatedly shown. The successes have occurred under circumstances which point to the procedure as the therapeutic agent. We have used lipiodol in 85 cases of sterility and have noted the production of morbidity in only one patient, who developed an acute exacerbation of an old pelvic inflammatory process (Case 3). We believe that if contraindications are scrupulously observed, the use of lipiodol is attended by negligible morbidity. The discovery of a more readily absorbable radiopaque substance would undoubtedly diminish the ill effects described in many reports where lipiodol has remained in situ in enclosed cavities over prolonged periods.

SUMMARY AND CONCLUSIONS

1. Observations are recorded based on the investigation of the tubal patency test as a therapeutic measure in sterility.

2. In a series of 133 patients in whom the patency test could be evaluated, 54, or 40.6 per cent became gravid.

3. In 114, or 85.7 per cent, of the patients where patency in one or both tubes was demonstrated, 51, or 45 per cent, conceived. In 19, or 14.3 per cent, of the patients in whom no patency was demonstrated to gas or oil, 3, or 15.8 per cent, conceived.

4. Twenty-eight, or 21.5 per cent, patients became pregnant within two months of the test, the pregnancy being attributable directly to the procedure.

5. Coitus immediately preceding insufflation probably added to the high percentage of successes and was attended by no ill effects.

6. An analysis of the pathologic conditions which contribute to tubal obstruction is presented.

7. The cure of sterility in tubal obstruction is accomplished by a reestablishment of tubal function and patency due to the mechanical effects of pertubation.

8. The relative merits of insufflation and lipiodol instillation as therapeutic agents are considered. We believe that lipiodol instillation is superior to gas insufflation both from a diagnostic and therapeutic standpoint.

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DISCUSSION

DR. ROLAND S. CRON, Milwaukee, Wis.—In principle and practice I agree with the writers in all respects except that we do not routinely arrange that the patency test be preceded by coitus. This does not seem to have influenced the incidence of conception for as you will observe about 50 per cent of our sterile women became pregnant.

Dr. Reuben Peterson and his associates first reported the therapeutic value of this test in 1922 at the St. Louis meeting of the A. M. A. In that report I recorded the first pregnancy that had occurred immediately following a gas insufflation. The following year, 1923, at the San Francisco meeting we presented the results obtained in the study of 36 sterile women. Pregnancy occurred in 13, or 36 per cent, of the women who had been insufflated.

Since 1935 gas insufflation has been used on not more than one out of every five patients. My conversion to lipiodol was due to the fact that tubes found to be impervious to carbon dioxide repeatedly became patent to an oily substance at pressures below that used for gas insufflations. Second, more patients, and many of those previously insufflated, become pregnant. Third, peritoneal reactions to lipiodol when minimum quantities, 5 to 7.5 c.c., were introduced, were no more common than after gas. Fourth, one can learn more about the condition of the uterus, tubes, and ovaries than is the case with gas insufflations.

In 1929 a study of sterility patients who were treated with carbon dioxide insufflations showed an incidence of 25 per cent successful pregnancies. In 1938 a review of 100 patients in whom pregnancy might occur because of tubes proved patent by use of lipiodol, showed that 39 per cent conceived.

The present review which covers a period from 1936 to 1940 is based on the study of 123 sterile couples. Where tubes were normal and open in 55 patients, 33 pregnancies resulted. Where tubes were abnormal and open in 33 patients, 12

pregnancies resulted with two repeat pregnancies following subsequent lipiodol injections. Where tubes were normal but uteri were abnormal (9 patients: didelphic uterus 3, postoperative inversion 1, and submucous fibroma 5), 3 pregnancies resulted.

The age of 5 patients was beyond 40 years, and not any of these became pregnant. Two husbands were sterile. Ten patients had closed tubes. After considering all patients in whom pregnancy might occur, we find in this last group that 48, or more than 50 per cent, became pregnant following lipiodol injections. From the time of the lipiodol injection to the last menstrual period in 35, or 70 per cent, of the pregnant patients, less than one month up to four months intervened. To me this is the best proof of the efficacy of the procedure.

DR. J. MILTON SINGLETON, KANSAS CITY, MO.—I wonder whether the writers do not feel that the time of insufflation, immediately or shortly after coitus, might not lead to increased incidence of ectopic and ovarian pregnancy. I have selected for my insufflations the fourth or fifth day after menstruation, when there is no danger of blowing the sperm up into the tube and consequent danger of producing an ectopic pregnancy.

I believe with the widely increasing use of vaginal plugs at menstruation that we are going to see a marked increase in the incidence of retrograde menstruation, chemical salpingitis, and hence in the incidence of sterility.

DR. SOLOMON (closing).—We do not believe that there is a higher incidence of ectopic pregnancy following the therapeutic use of gas or oil. In our series there were two instances of tubal pregnancy following pertubation.

We do not believe that lipiodol is irritating to the peritoneum if proper contraindications to the test are observed. Forsdike of London reports many laparotomies performed from a few days to a few years after the use of lipiodol, and in none did he observe any evidence of peritoneal irritation. Most of the oil is absorbed in a week or ten days, and a flare-up may occur only when there is obscure acute or subacute inflammatory disease present.

We can account for no instance of infection attributable to the preliminary coitus in our series, and feel that it is important therapeutically.

THE OCCURRENCE OF DIPHTHERIA ANTITOXIN IN THE HUMAN PREGNANT MOTHER, NEWBORN INFANT, AND THE PLACENTA*

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INTRODUCTION

MUCH has been written on the placental transfer of antibodies. As early as 1879 Burckhardt[1] attempted to protect the fetus against variola by vaccination of the pregnant mother. He felt that intrauterine vaccination would protect the infant against smallpox.

Fischl and Wundscheim[2] on examining cord blood found diphtheria antitoxin present in a good proportion of specimens. In 1904 Polano[3] reported on a study of the passive transfer of diphtheria antitoxin from mother to child. He found that, by giving the pregnant mother antitoxin some days previous to delivery, he was able to demonstrate the presence of the antitoxin in the cord blood. Staubli,[4] von Groer and Kassowitz[5] and numerous other investigators have demonstrated that antibodies are transferred to the fetus whether the mother is actively or passively immunized. In spite of the abundance of evidence of the placental transfer of antibodies, some of the earlier investigators were of the opinion that such transfer did not occur through a normal placenta and that the antibodies found in fetal blood were produced by fetal tissues. Bourquin's[6] work on the permeability of the placenta to agglutinins, hemolysins, diphtheria antitoxin and diastase has done much to disprove this concept of the earlier investigators. Kuttner and Ratner[7] in addition to confirming the permeability of the human placenta to antibodies, showed that the ingestion of colostrum did not increase the antibody content in the blood stream of the infant. More recent contributions to this line of investigation have been made by Ogawa,[8] who found that the amount of antitoxin in the sera of the offspring of actively immunized rabbits was proportional to that in the mother; by Richardson,[9] who demonstrated the presence of diphtheria antibacterial antibodies as well as antitoxin in mothers and offspring of guinea pigs actively immunized against diphtheria and by Neill, Gaspari, Richardson and Sugg[10] who studied the diphtheria antibacterial antibodies and antitoxin in a mother with an unusually high degree of immunity and found that the diphtheria-antibacterial antibodies, as well as the antitoxin, were transmitted to the infant if present in the mother.

The fact that the placenta acts as a "go between" for the transmission of antibodies from the maternal to the fetal side raises many questions. It is of interest to determine to what extent the placenta is permeable to antibodies circulating in the maternal blood stream; whether such antibodies are transferred to the fetus in equal strength or are filtered out in passing through the placenta; to what extent, if at all, the placenta retains such antibodies and whether it is possible that placental tissue may have the property of antibody formation when properly

*Read at the Chicago Gynecological Society, November 15, 1940.

stimulated. There is also the question as to whether active immunization of the pregnant mother will result in active immunization of the fetus in utero and, if so, how long will such immunity persist after birth. Since there is a general increased activity of the bodily functions during pregnancy, the possibility exists that antibody formation might also be stimulated.

In order to obtain an answer to some of the foregoing questions, and because the diphtheria antitoxin level in the human pregnant mother has been followed through pregnancy only in isolated instances, and as far as is known, active immunization of the human pregnant mother has not been attempted in order to determine the effect on the mother, newborn infant, and the placenta, the following experiments were carried out.

METHODS

The subjects chosen for this problem were in the latter part of the second trimester of their pregnancy. All mothers were Schick tested on admission, 0.1 c.c. of the standard Schick test toxin being used. All Schick tests were controlled with heated toxin. At the same time that the patient received the Schick test, blood was obtained from the cubital vein for the determination of the diphtheria antitoxin titer. The Schick tests were read at the end of seventy-two hours and again at the end of a week. Schick positive and Schick negative mothers were actively immunized with diphtheria toxoid and an equal number were used as a control. The mothers immunized received five subcutaneous injections at weekly intervals, beginning with 0.1 c.c., then 0.25, 0.5, 1.0, and 2.0 c.c., respectively, of the diphtheria toxoid. Blood determinations for diphtheria antitoxin were made at monthly intervals so that each patient had three or four determinations by the time of delivery of the newborn infant. Upon delivery, fetal blood was obtained from the umbilical cord for diphtheria antitoxin determinations.

Diphtheria antitoxin determinations were also made on a group of non-Schick tested, nonimmunized mothers followed through their course of pregnancy as a control on the stimulating effect of the Schick test material.

The infants were Schick tested some time during the first week of life, usually on the sixth day.

The tests for diphtheria antitoxin were made by the intracutaneous test in rabbits, using the Moss-Jones modification of the test reported by Fraser.[11]*

Immediately following delivery of the newborn infant, the placenta was emptied of its residual blood as completely as possible. This was carried out by frequently stripping the placental cord, 50 to 125 c.c. of blood usually being obtained.

Each placenta was weighed and then extracted according to the method of McKhann.[12] Briefly the method is as follows:

The placenta is ground in a meat grinder and extracted with a 4 per cent salt solution. The mixture of placental tissue in salt solution is passed through cheesecloth and the filtrate centrifuged. After centrifugation, ammonium sulfate is added to make a 50 per cent saturation. This results in the precipitation of the globulins. The precipitate is dialized, filtered, and passed through a Berkefeld filter. Diphtheria antitoxin determinations were made on the final filtrate.

RESULTS

Schick Tests.—Fifty-two and eight-tenths per cent of the mothers gave a positive Schick test. A small number gave a pseudoreaction. In a few of the patients, there was a combined Schick reaction. Only a small number of those Schick tested reacted rather severely to the test. They complained of an intense itching and de-

*These tests were carried out by Eli Lilly & Company Research Laboratories.

veloped a rather marked erythema, followed by vesiculation, desquamation, and pigmentation. The blood serum diphtheria antitoxin determinations were found to be in accord with the Schick test results. Schick positive individuals contained 0.002 of a unit or less of diphtheria antitoxin per cubic centimeter of blood serum. This confirms the work of Brandon and Fraser[13] who have shown that the antitoxin blood level for Schick-immunity lies between 0.002 and 0.004 of a unit of antitoxin per cubic centimeter of serum.

Nonimmunized Mothers and Infants.—The results of the control group of nonimmunized mothers with positive Schick tests showed a low antitoxin content in the blood. The titer remained at the same level throughout the pregnancy in all but one patient (Table I). In Case 9, there was some rise in the antitoxin level as pregnancy neared term.

Fraser and Halpern,[14] reporting on a group of Schick positive nonimmunized adults, found that there was no rise in the antitoxin-level when it was 0.002 of a unit or less per cubic centimeter of serum. They feel that Schick positive and nonimmunized individuals developing a rise in the titer level are exceptions and that these persons have amounts of antitoxin which are not detected at the 0.002th level of titration. Case 9 would have to be classed as such an exception, as this patient had a positive Schick, 0.002 of a unit of diphtheria antitoxin per cubic centimeter of serum at seven months, 2.0 units at eight months, 2.0 units at nine months, and 2.0 units at term.

Schick positive mothers, showing no change in the antitoxin titer during the course of their pregnancy, gave birth to infants that were Schick positive and whose antitoxin level was the same as that of the mother (Table I).

TABLE I. DIPHTHERIA ANTITOXIN LEVELS IN NONIMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
1	–	+	0.002	0.002	0.002	0.002	13	0.002	+
3	–	+	0.002	0.002	0.002	0.002	11	0.002	+
5	–	+	0.002	0.002	0.002	0.002	11	0.002	+
6	–	+	0.002	0.002	0.002	0.002	13	0.002	+
9	–	+	0.002	2.0	2.0	2.0	10	1.0	±
12	–	+	0.002	0.002	0.002	0.002	14	0.002	+
15	–	+	0.002	0.002	0.002	0.002	16	0.002	+
16	–	+	0.002	0.002	0.002	0.002	18	0.002	+
17	–	+	0.002	0.002	0.002	0.002	23	0.002	+
28	–	+	0.002	0.002	0.002	0.002	11	0.002	+
31	–	+	0.002	0.002		0.002	12	0.002	+

*"u" equals units of antitoxin.

The antitoxin titer of the controls with negative Schick tests showed a gradual increase in the antitoxin level as pregnancy neared term (Cases 4, 8, 11, 13, etc., Table II). Some of the patients showed a decrease in the antitoxin level before term (Cases 2, 10, 23, and 26, Table II) and in only two instances (Cases 7 and 20) did that decrease fall below the level of the first determination.

Control mothers with negative Schick tests gave birth to infants with negative Schick tests and an antitoxin level equal to (Cases 4, 11, 14, etc.), higher (Cases 2, 7, 13, 20, etc.), and, in two patients (Cases 8 and 19), lower than that of the mothers' blood at term. The antitoxin level of the infants in these cases was always higher than the preliminary antitoxin level of the mother.

The rise in the antitoxin titer level during the course of pregnancy in the control group of mothers may be attributed to the accelerating effect of the toxin in the

TABLE II. DIPHTHERIA ANTITOXIN LEVELS IN NONIMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
2	+	−	0.1	0.1	0.5	0.2	11	1.0	−
4	Exposure	±	0.01	1.0	1.0	1.0	14	1.0	−
7	−	−	0.01	1.0	0.5	0.002	14	1.0	−
8	−	−	0.2	1.0	0.5	1.0	13	0.5	−
10	−	+	0.01	2.0		1.0	9	Stillbirth	
11	−	−	0.01	2.0		2.0	10	2.0	−
13	−	±	0.01	2.0	2.0	2.0	15	5.0	−
14	−	−	0.1	0.2		0.2	10	0.2	−
18	−	−	0.01	2.0		2.0	20	Stillbirth	
19	−	±	0.1	1.0		1.0	22	0.5	−
20	−	±	0.2	10.0	10.0	0.1	11	10.0	−
21	−	±	0.01	1.0	1.0	1.0	20	2.0	−
22	−	±	0.1	2.0		2.0	19	2.0	−
23	−	−	0.05	2.0	1.0	1.0	13	2.0	−
25	−	−	0.005	1.0		1.0	8	1.0	−
26	+	−	0.1	5.0		1.0	26	2.0	−
27	−	−	0.05	0.05	0.05	0.1	21	0.1	−

*"u" equals units of antitoxin.

TABLE III. DIPHTHERIA ANTITOXIN LEVELS IN NON-SCHICK TESTED NONIMMUNIZED MOTHERS

Units per c.c. Serum
Diphtheria Antitoxin Titer Level

CASE	7 MO.	8 MO.	9 MO.
1	0.2	0.2	0.2
3	0.2	0.2	0.2
4	0.5	0.5	0.5
5	0.02	0.02	0.02
9	0.2	0.2	0.2
10	0.2	0.2	0.2
13	0.1	0.1	0.1
2	0.002	0.002	0.002
6	0.002	0.002	0.002
7	0.002	0.002	0.002
8	0.002	0.002	0.002
11	0.002	0.002	0.002
12	0.002	0.002	0.002

Schick test material. This was borne out by the results obtained on a small group of non-Schick tested, nonimmunized mothers followed during their course of pregnancy. In this group, as illustrated by Table III, there were no changes in the antitoxin level. This is in accord with the investigations of Fraser and Halpern[14] who found that Schick material stimulates antitoxin production in individuals with an antitoxin level greater than 0.002 of a unit per cubic centimeter of serum and that the response, when it occurs, is rapid. This fact is well illustrated by the findings shown in Table I. These investigators also found that non-Schick tested, nonimmunized individuals, possessing natural antitoxin, gave no change in the titer level over a period of years.

From the above, it can be stated that the transfer through the placenta of natural diphtheria antitoxin, when possessed by the mother, will provide the newborn infant

TABLE IV. DIPHTHERIA ANTITOXIN LEVELS IN ACTIVELY IMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
1	–	+	0.002	0.002	0.01	0.002	10	0.02	–
2	–	+	0.002	1.0	1.0	0.5	16	0.002	–
6	–	±	0.002	5.0	0.1	5.0	12	5.0	–
7	–	+	0.002	0.1	0.2	0.2	17	0.2	–
12	–	+	0.002	10.0	5.0	1.0	17	5.0	–
13	–	+	0.002	0.002	0.02	0.002	12	0.002	–
15	–	–	0.002	0.1	0.2	0.2	11	0.2	–
16	–	+	0.002	10.0	5.0	5.0	15	10.0	–
18	–	+	0.002	0.002	0.002	0.01	14	0.01	–
21	–	+	0.002	0.1	0.2	0.2	18	0.5	–
24	–	+	0.002	0.05	0.1	0.1	15	0.2	–
25	–	+	0.002	0.002	0.01	0.01	18	0.002	–
29	–	+	0.002	0.002		0.002	10	0.002	–
31	–	+	0.002	0.002	0.005	0.02	20	0.02	–

*"u" equals units of antitoxin.

with a passive immunity. It is also apparent that the mere Schick testing of the pregnant mother possessing natural antitoxin will act in most cases as a stimulus to increase antitoxin production and provide possibly a greater and more prolonged protection to the infant after birth.

Immunized Mothers and Infants.—In the actively immunized group of mothers with positive Schick tests, the antitoxin response varied with each individual as regards the rapidity and quantity of the increase. In most instances (Table IV),

TABLE V. DIPHTHERIA ANTITOXIN LEVELS IN ACTIVELY IMMUNIZED MOTHERS AND NEWBORN INFANTS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	HISTORY OF DIPHTHERIA	SCHICK TEST	ORIGINAL TITER	8 MO.	9 MO.	TERM	WEEKS AFTER DETERMINATION	FETAL BLOOD	SCHICK TEST ON INFANT
3	–	±	0.2	50.0	50.0	20.0	15	50.0	–
4	–	–	0.01	50.0		50.0	8	20.0	–
5	–	–	0.01	50.0		10.0	8	20.0	–
8	carrier	–	0.1	10.0		5.0	21	5.0	–
9	–	–	0.1	20.0	20.0	20.0	20	20.0	–
10	–	–	0.01	10.0		5.0	10	10.0	–
11	–	±	0.1	50.0	10.0	10.0	13	20.0	–
14	–	–	0.0	20.0	20.0	20.0	11	20.0	–
17	–	±	0.1	50.0		20.0	10	20.0	–
19	–	–	0.2	100.0		50.0	22	100.0	–
20	–	–	0.5	20.0	20.0	20.0	19	50.0	–
22	–	–	0.2	10.0	5.0	5.0	16	10.0	–
23	–	–	0.2	5.0		5.0	13	5.0	–
26	–	–	0.05	10.0		10.0	27	10.0	–
27	–	–	0.2	10.0		10.0	25	10.0	–
28	–	+	0.2		10.0	10.0	22	10.0	–
30	–	–	0.2	20.0		20.0	16	20.0	–
32	–	±	0.2			50.0	8	50.0	–
33	–	–	0.1	5.0		10.0	12	20.0	–
34	–	±	1.0		20.0	10.0	12	20.0	–

*"u" equals units of antitoxin.

there was a rise in the antitoxin titer at term, this being 5 to 2,500 times that of the original titer. In only two patients (Cases 13 and 29) was there no rise in the antitoxin concentration in the blood serum of the mothers followed during their course of pregnancy.

The Schick negative mothers showed a hyperactive response to antibody formation. All mothers (Table V) had a high antitoxin titer at term. This increase varied from 50 to 5,000 times the original titer value. In some cases, this increase remained throughout pregnancy (Cases 4, 9, 14, 20, Table V) and in others, it was depleted at term but was never back to the pre-immunization value (Cases 5, 10, 17, Table V).

The length of time elapsing between the first immunizing dose of toxoid and the last diphtheria antitoxin titer determination in the Schick positive and Schick negative group of mothers, apparently, played no part in the quantity of antitoxin formed, as the maximum concentration in both was reached in four to eight weeks after immunization was begun (Cases 6 and 31, Table IV, and Cases 4 and 27, Table V). This is not in accordance with the general opinion that the peak of immunity is attained in three to six months.

The infants born to the actively immunized Schick positive and negative mothers gave negative Schick tests and in most instances had an antitoxin titer level equal to that of the mothers at term (Tables IV and V).

Placental Extracts.—Antitoxin determinations were made upon placental extracts of both immunized and nonimmunized mothers to determine, if possible, whether the placenta acted merely to transfer substances to the fetus, whether antibodies are stored in its tissue, or whether the tissue itself is capable of antibody formation when properly stimulated.

TABLE VI. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE NONIMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	MATERNAL DIPHTHERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLACENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOTAL UNITS OF DIPH. ANTITOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD ≃ TO TOTAL PLACENTAL UNITS
1	<0.002	<0.002	<0.002	450.4	0.0000	0.000	0.0
3	0.002	0.002	0.002	630.0	0.0005	0.315	157.5
5	0.002	0.002	0.002	463.0	0.0008	0.370	185.2
6	<0.002	<0.002	0.002	462.0	0.0017	0.785	392.7
9	2.0	1.0	0.2	466.3	0.0514	23.96	23.96
12	<0.002	0.002	<0.002	770.0	0.0000	0.000	0.00
17	<0.002	<0.002	0.002	638.8	0.0014	0.910	455.0
28	<0.002	<0.002	0.002	527.8	0.0014	0.76	380.00

*"u" equals units of antitoxin.

In the Schick positive nonimmunized group of mothers that had 0.002 units or less of antitoxin per cubic centimeter of blood (Table VI), the amount of antitoxin per gram of placenta corresponded, in most cases, very closely to the amount present in the maternal and fetal blood. In only 3 cases (6, 17 and 28) was a small amount of antitoxin found in the placenta when none was detectable in the maternal or fetal blood. This could probably be explained by the fact that the antitoxin in the placental extract is increased in concentration as a result of the method of extraction.

TABLE VII. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE NONIMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	MATERNAL DIPHTHERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLACENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOTAL UNITS OF DIPH. ANTITOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD ≃ TO TOTAL PLACENTAL UNITS
2	0.2	1.0	0.02	717.5	0.009	6.6	6.6
4	1.0	1.0	0.1	516.4	0.061	31.75	31.75
8	1.0	0.5	0.5	446.0	0.357	159.22	318.44
11	2.0	2.0	0.2	513.8	0.144	74.14	37.07
13	2.0	5.0	0.5	660.0	0.355	221.6	44.32
14	0.2	0.2	0.05	562.1	0.039	22.24	111.2
19	1.0	0.5	0.2	464.4	0.157	73.3	146.6
20	0.1	10.0	1.0	707.8	0.492	348.23	34.82
21	1.0	2.0	0.1	528.2	0.096	40.97	20.48
22	2.0	2.0	0.02	432.0	0.019	8.47	4.23
23	1.0	2.0	0.2	684.9	0.111	76.64	38.32
25	1.0	1.0	0.2	521.7	0.207	108.5	108.5
26	1.0	2.0	0.1	474.7	0.096	45.8	22.9

*"u" equals units of antitoxin.

In the nonimmunized Schick negative group that contained 0.002 units of antitoxin or more per cubic centimeter of blood serum, the amount of antitoxin per gram of placenta was very small in all cases (Table VII), except one, as compared with the number of units per cubic centimeter in the maternal and fetal blood. Case 20 had about five times more antitoxin per gram of placenta than the maternal blood, but had one-twentieth that of the fetal blood. This is the only case also in which there was an excessively greater amount of antitoxin in the fetal blood than in the maternal blood. When the average amount of diphtheria antitoxin in the blood serum of all the mothers is compared with the average amount of antitoxin in all of the placenta, the blood serum possesses about sixteen times as much antitoxin per cubic centimeter of blood serum as the placenta does per gram of tissue.

These results indicate that the placenta normally contains only small amounts of diphtheria antitoxin and that in those mothers in whom there was no increase in the blood antitoxin during pregnancy, the amount per gram of placenta more closely approximates the amount per cubic centimeter of blood serum than in those in which there was a slight rise.

The results on the actively immunized mothers present much the same picture (Tables VIII and IX). In the Schick positive group, which had original titers of 0.002 units or less, there was an average of about 7.8 times as much antitoxin per cubic centimeter of blood serum as in 1 Gm. of placental tissue. In the actively immunized group of Schick negative mothers having original titers of 0.002 units or more, the serum contained an average of fourteen times as much antitoxin per cubic centimeter as did 1 Gm. of placenta.

There is very little evidence in these results to indicate that the placenta either stores or forms appreciable amounts of diphtheria antitoxin following active immunization. The amount of antitoxin in the placenta rises following immunization but not in proportion to the rise in the antitoxin level of the blood. In fact, in many cases, the total amount of antitoxin in the placenta can be accounted for on the basis of the retention of a small amount of fetal and maternal blood, since it was impossible to remove the blood completely from the placenta. With increase in the blood serum level, this factor becomes more appreciable. Cases 2, 13, 18, 21, and

29 (Table VIII) are the only ones in which the placenta contained more antitoxin per gram than did the fetal or maternal blood. These results suggest that occasionally a placenta may store (or form) a small amount of antitoxin. Furthermore, a slight amount of storage could easily be obscured by the enormous increase that occurs in the blood of some of the actively immunized mothers.

TABLE VIII. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE ACTIVELY IMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level 0.002 u/c.c.* Serum or Less

CASE	MATERNAL DIPHTHERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLACENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOTAL UNITS OF DIPH. ANTITOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD ≃ TO TOTAL PLACENTAL UNITS
1	0.02	0.02	0.01	433.0	0.008	3.4	170.0
2	0.5	<0.002	0.2	397.2	0.055	22.0	11000.0
6	5.0	5.0	1.0	448.6	0.490	220.0	44.0
7	0.2	0.2	0.1	572.4	0.008	4.98	24.9
12	1.0	5.0	0.2	492.4	0.136	67.1	13.42
13	0.002	<0.002	0.01	681.2	0.002	2.0	1000.0
15	0.2	0.2	0.2	593.6	0.086	51.0	255.0
16	5.0	10.0	0.5	542.2	0.533	300.0	30.0
18	0.01	0.01	0.1	598.4	0.095	55.5	5550.0
21	0.2	0.5	0.5	619.6	0.34	211.5	423.0
24	0.1	0.2	0.01	496.7	0.008	4.29	21.45
29	<0.002	<0.002	0.002	568.2	0.001	0.99	496.0
31	0.02	0.02	0.002	519.1	0.001	0.93	46.7

*"u" equals units of antitoxin.

TABLE IX. A COMPARISON OF THE MATERNAL, FETAL AND PLACENTAL ANTITOXIC VALUES IN THE ACTIVELY IMMUNIZED GROUP OF PREGNANT MOTHERS

Original Antitoxin Titer Level > 0.002 u/c.c.* Serum

CASE	MATERNAL DIPHTHERIA ANTITOXIN TITER U/C.C. SERUM AT TERM	FETAL DIPH. ANTITOXIN TITER U/C.C. SERUM AT BIRTH	DIPH. ANTITOXIN TITER U/C.C. OF PLACENTAL EXTR.	GRAM WT. OF PLACENTA	DIPH. ANTITOXIN TITER U/GM. PLACENTAL TISSUE	TOXIN IN THE PLACENTA	C.C. OF FETAL BLOOD ≃ TO TOTAL PLACENTAL UNITS
3	20.0	50.0	5.0	485.4	2.15	1045.0	20.9
4	50.0	20.0	2.0	525.0	1.35	710.0	35.5
5	10.0	20.0	1.0	556.5	0.287	160.0	8.0
8	5.0	5.0	1.0	489.4	0.868	425.0	85.0
9	20.0	20.0	1.0	442.4	0.96	425.3	21.2
10	5.0	10.0	0.5	349.4	0.49	170.8	17.08
11	10.0	20.0	0.002	600.4	0.0015	0.929	0.046
14	20.0	20.0	5.0	448.4	1.78	800.0	40.0
17	20.0	20.0	5.0	581.0	1.24	724.0	36.25
19	50.0	100.0	10.0	490.4	9.31	4566.6	45.66
20	20.0	50.0	2.0	688.9	1.48	1020.0	20.4
22	5.0	10.0	1.0	609.1	0.87	532.6	53.26
23	5.0	5.0	1.0	550.8	0.76	420.0	84.0
32	50.0	50.0	5.0	547.0	3.2	1755.0	35.1
33	10.0	20.0	1.0	529.0	0.72	381.3	19.06
35	10.0	20.0	1.0	450.9	0.86	390.0	19.5

*"u" equals units of antitoxin.

DISCUSSION

It was the intention of this investigation to determine the part played by the placenta in the transfer of diphtheria antitoxin from the nonimmunized and actively immunized human pregnant mother to her offspring and also to evaluate placental extracts as a source of antibody.

It was found that the placentas of the nonimmunized and immunized group of mothers were permeable to the circulating antitoxin of the mother and it was passed on to the fetus, in nearly all cases, in equal strength. As the literature reveals, this fact has been observed and pointed out for a number of years.

Although many mothers possess natural antitoxin, it is of a low value. If the duration of prophylaxis is dependent upon the amount of circulating antibodies, the mere Schick testing of the mothers possessing a Schick-immunity level, will result in a rise in the antitoxin concentration. This in turn will be transferred to the newborn and will probably provide a more lasting passive immunity.

The marked increase in the antitoxin concentration of the blood serum of the actively immunized mothers and its transfer to the infant will certainly provide a more lasting immunity to the newborn. Whether we have succeeded in the active immunization of the fetus in utero by actively immunizing the pregnant mother is impossible to determine at the present time. More information on this question will become available, it is hoped, after the newborn infants have been followed over a period of one to two years.

The results on the placental extracts were exceedingly interesting, inasmuch as placental extracts have been extensively used as a prophylactic against measles.

It was found that the placenta of nonimmunized and actively immunized mothers contained very little diphtheria antitoxin when compared to the amount present in the blood serum of the mother and that this amount, in most cases, could easily be accounted for by residual maternal-fetal blood in the placenta. This fact may well account for the value attached to the placental extracts for measles immune globulin as in this extract, as described by McKhann,[12] the placenta is not emptied of its retained blood but it is included in the extract. Possibly the protective value that might be derived from such an extract could be obtained by merely using convalescent serum or pooled adult whole blood, as Grod[15] found that retroplacental blood exercised the same influence on the course of measles as did serum from adults or placental extract.

CONCLUSIONS

1. Nonimmunized, Schick positive mothers showed no rise in the antitoxin level during their course of pregnancy.

2. Nonimmunized, Schick negative mothers all showed a rise in the antitoxin content during their course of pregnancy.

3. Infants born to Schick positive mothers were usually Schick positive and had an antitoxin content, in most instances, equal to that of the mothers at term.

4. Schick positive and negative mothers, actively immunized, showed a marked response in the formation of antitoxin, in some cases as much as 5000 times the pre-immunization level being reached.

5. Infants born to the actively immunized mothers gave negative Schick tests and had antitoxin level, in most cases, equal to that of the mothers at term.

6. The maximum antitoxin level in the mothers' blood was reached in a period of four to eight weeks.

7. Relative "blood free" placentas of immunized and nonimmunized mothers, when extracted for diphtheria antitoxin, yielded, in most cases, insignificant amounts.

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DISCUSSION

DR. ROBERT A. BLACK.—The diphtheria question is by no means settled. Bieber immunized 1,097 children out of a group of 3,000 and found four who contracted the disease. Greengard in his studies felt that the giving of toxoid before three months of age did very little good. Eighty-four per cent of fetuses at birth have been found to have antitoxin in the blood, a figure that falls off gradually until at eighteen months it was 32 per cent, and at two and one-half years it was 28 per cent. With these figures in mind you wonder whether trying to immunize through the mother would be really worth while.

In order to find out whether Dr. Schmitz was doing something that was rather useless, I looked up some death rates. There are 49,000 to 50,000 infants born in Chicago each year. During the past ten years we had 2 deaths in Chicago from diphtheria in infants under six months. Incidentally there have been no deaths from diphtheria in the six-month-old infants in four years. In looking up the incidence of diphtheria in the yearling, we found that there were 251 cases of diphtheria with 36 deaths. If Dr. Schmitz can immunize these babies he has made a great step forward.

If Dr. Schmitz could get whooping cough antibodies to be effective through the placenta he will have made another contribution to pediatrics.

One thing occurred to me that might explain some of the discrepancies in the report. Dr. Schmitz noted, for example, in No. 9, from $\frac{1}{200}$ to $\frac{1}{25}$ unit of toxin in the blood. I wonder if he took a culture on the mother's throat, for the mother might have acquired diphtheria.

There is a great deal of talk of colostrum being one of the fluids that carries immunizing bodies or antibodies into the infant. It would be interesting to check this point.

DR. JAMES CONNER.—It is a bit out of the ordinary to find 52 per cent of positive Schick tests in adults. The majority of workers insist that at least 90 per

cent of adults are immune to diphtheria. Most of us accept that premise. That is why many say that it is impossible for a child under six months of age to have diphtheria, because it has been passively immunized by the mother.

Did the mothers who became Schick negative have small doses of toxoid? This question arises from an interesting parallel. There is available at the present time a tetanus toxoid which can be given to an individual in divided doses. If such a patient receives subsequently a contaminated wound, it is not necessary to administer tetanus antitoxin. Instead we can give the patient an injection of tetanus toxoid and immediately the titer rises. This is possible because the incubation period for tetanus is longer than that for diphtheria. It may be desirable to administer the combination toxoids to protect against diphtheria and tetanus.

Furthermore, it was significant that the highest blood titer level was obtained in the period between four and eight weeks. That bears out the work we are doing at the Municipal Contagious Disease Hospital. We administer to adults with positive Schick tests $\frac{1}{10}$ c.c. of toxoid intradermally. We observed in a large number of these patients that the Schick test became negative at the end of three weeks. The ordinary procedure is to give toxoid subcutaneously, at intervals of one month and hope to get a negative Schick in six months. I would like to ask whether this $\frac{1}{10}$ c.c. had been given through the skin. Perhaps the patients may have received what is equivalent to an intradermal dose of toxoid. This method is used in adults who would be made uncomfortable with subcutaneous injections. The systemic reactions are much less with $\frac{1}{10}$ c.c. intradermally.

We have used placenta extract in an endeavor to control an outbreak of measles. In our last epidemic of measles we used normal human serum in 40 c.c. doses, placenta extract in 2 c.c. doses, and in a third group convalescent measles serum in doses depending upon the age. The convalescent measles serum was more effective than pooled human serum. The placenta extract was of the least value. In the majority of instances we did not protect the child against a typical attack when placenta extract was used. At the Contagious Hospital, we desire to prevent the patient from developing measles.

The problem of whooping cough in infants under one year is of considerable magnitude. I wonder if the obstetricians might give the mother a little pertussis vaccine and save us some trouble.

DR. FREDERICK H. FALLS.—In 1924, working with colon bacillus pyelitis of pregnancy, we showed that immune bodies developed in the mother in response to the infection were transferred to the fetal blood, and that the titer of the agglutinins in the fetal blood was almost the same as the titer of the agglutinins in the mother's blood. Previous to that I had found that in asthma the substances which stimulate eosinophilia were transferred to fetal blood. Since then I have found eosinophilia in three other babies born to mothers with asthma. It is quite significant that these substances are manufactured by the mother and pass through the placenta into the fetal blood. In pyelitis, the causative organism is bound to get into the vagina in large numbers during labor. After rupture of the membranes these organisms will invade the uterus and placenta and secondarily infect the fetus. We would probably have fatal results in a large percentage of the cases were it not for the mobilization of protective agglutinins.

DR. LIEBLING (closing).—Dr. Black's question, whether the infant will be protected during the first six months of life following active immunization of the pregnant mother, may be answered in the affirmative. At present, I have followed a group of these infants beyond the sixth month of life and found that children born to actively immunized mothers presented a negative Schick test at the age of eight or nine months. Of greater interest is the transfer of passive immunity to the infant from a group of Schick-negative nonimmunized mothers. This may be attributed to the stimulating effect of the toxin in the Schick test material, as the offspring of this group of mothers also responded negatively to the test eight or nine months after birth. I, therefore, feel that Schick testing alone without active immunization of the mother has acted to protect the infant during the first nine months of life.

The transfer of antitoxin by way of the colostrum was also investigated, a report of which will be presented in the near future. It was interesting to note that the colostrum of nonimmunized and actively immunized mothers possessed very little antitoxin, and therefore, offered a very minor source of antibody transfer to the infant. This is best illustrated by some of the actively immunized mothers possessing an antitoxin titer of 50 to 100 units per cubic centimeter of serum, yet transferring to the infant only 0.1 unit or less of antitoxin per cubic centimeter by way of the colostrum. An article by Kuttner and Ratner bears out this finding.

As to the discomfort offered the patient with the doses of toxoid administered, it may be stated that the Schick-positive mothers complained very little of any reaction, whereas, occasionally, the Schick-negative mothers, receiving the routine dosage of toxoid, complained of painful arms and headaches.

The value of the Schick test as a stimulus for increased antitoxin formation in an already Schick-negative mother is illustrated by the following case: The mother of two children was Schick tested during the course of her third pregnancy, and the response was negative. I Schick tested the infant at nine months of age and also the two-year-old child who had not received any previous Schick test or immunization against diphtheria. The infant responded negatively to the test, whereas, the two-year-old child presented a definite positive reaction.

Whether the children of actively immunized pregnant mothers have been actively or passively immunized in utero is rather difficult to state, as at present, no method exists which differentiates active from passive immune bodies.

PITUITRIN SHOCK*

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IT IS imperative that untoward reactions following the use of a drug of established clinical value receive critical and precise scrutiny in order that such undesirable reactions may be avoided. A valuable therapeutic adjuvant might unnecessarily be discarded because of the fear of side effects which may be obviated or properly combated through a fuller appreciation of the pharmacologic actions and through a more intelligent usage of the offending drug.

These remarks, truisms applicable generally to all therapeutic agents, are pointed in this paper particularly to posterior pituitary preparations which have an accepted place in the armamentarium of obstetrics and gynecology chiefly, and to a lesser extent, in general surgery and internal medicine. The untoward reaction with which we are concerned primarily is that of "shock" appearing after the administration of a posterior pituitary preparation. "Pituitrin shock" is an infrequent but no longer rare experience as observed by a study of the literature. Its occurrence has received but passing mention in the standard textbooks on obstetrics and gynecology.[1]

A review of the literature rewards one with isolated case reports. The earliest paper of interest is that of Hasson[2] who described a case of pituitary dysfunction being treated with posterior pituitary extract. After some period of repeated administration, the patient developed pruritus and angioneurotic edema following the injection of the preparation. While this case did not present evidence of shock, it is of interest because it served to describe pituitrin hypersensitivity which, in later re-

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ports, was found to be an etiologic factor in shock following pituitrin administration. Wang and Maxwell in 1933[3] reported a case of anaphylaxis following the intramuscular injection of 1 c.c. of posterior pituitary extract in a patient during labor, as evidenced by intense pruritus, urticaria, and shock; recovery was effected by intravenous fluids and intravenous digitalis. This case is of particular interest because it raises the possibility of sensitization by previous administration of posterior pituitary preparations, as this patient had received such agents during her previous deliveries.

Since this report there have been several further cases[4] described. These cases follow a somewhat similar pattern of events which may be described briefly as follows: the patient, in the second or third stage of labor, was given a hypodermic or intramuscular injection of a posterior pituitary preparation of a dosage varying from minims ii to 1 c.c.; within ten to thirty minutes angioneurotic edema, urticaria, dyspnea, and shock appeared. In a number of cases no shock appeared, with urticaria, pruritus, and angioneurotic edema as the major complaints. Adrenalin was found to be effective in relieving the symptoms in all cases. Those reports which included skin tests described their patients as sensitive to the extracts used; also, most of the cases revealed a history of some previous administration of the extract.

Not all reports are found in obstetric cases. Seed and others[5] described a case of shock, in an elderly man with diverticulitis, following the injection of pituitrin; no skin tests were reported. Potter[6] mentioned the occurrence of shock in 10 cases out of 1,200 who had received pituitrin for varying surgical conditions; no deaths occurred and all patients responded to fluids and adrenalin. No details were given.

Our experiences with pituitrin shock have been quite unique and undescribed, in that all our cases occurred while the patient was under surgical anesthesia. During the past year 7 cases have been observed demonstrating shock almost immediately after the injection of a posterior pituitary preparation (surgical and obstetrical pituitrin). These cases are reported to emphasize the danger of pituitrin shock and to discuss the mechanism of such reactions with a view toward careful and intelligent use of the drug and toward a rational therapy.

Of the 7 cases observed, 2 are herewith presented in some detail, being representative of our entire group.

CASE 1.—M. C., a 43-year-old white female, was admitted for a vaginal hysterectomy to the gynecology ward service. Her preoperative condition was good. On the operative morning, the patient was given 1/6 gr. of morphine sulphate and 1/150 gr. of scopolamine, one and a half hours before the scheduled time of operation. The anesthetic agents were ethylene and ether, administered by the closed, carbon dioxide absorption technique; at no time did the depth of anesthesia exceed that of first plane. Blood pressure at the start of the operation was 100/64, and pulse 90. Two minutes after the start of the operation, 1 c.c. of surgical pituitrin (20 pressor units) was injected intramuscularly in the arm in order to produce a less vascular operative field by virtue of its peripheral vasoconstrictor action. Within eight minutes the blood pressure could not be obtained; the pulse could be palpated with difficulty, being 60 per minute. The appearance of the patient was one of mild shock. During the remainder of the operation, a period of forty-five minutes, the blood pressure could not be obtained, while the pulse persisted between 48 and 54. Some forty-five minutes after the end of the operation, the blood pressure was found to be 110/70. Therapy consisted of 2,500 c.c. of 5 per cent glucose in saline intravenously. The patient's postoperative course was uneventful. Intradermal skin tests with surgical pituitrin (0.1 c.c. of undiluted and 1-10 dilution each) were negative.

The absence of significant hemorrhage and surgical trauma and the prompt appearance of shock following the administration of pituitrin point unequivocably to

the pituitrin as the responsible agent. The negative skin tests, performed with the preparation used, rule out anaphylaxis as the cause of shock. Of interest is the unusual combination of shock and bradycardia which this case demonstrated. This bradycardia has been observed experimentally after the administration of pituitrin and may be due to vagal stimulation, direct myocardial action or intense coronary constriction.[7]

CASE 2.—F. B., aged 29 years, was admitted in labor to the obstetric ward service. Two years before admission the patient had been subjected to a cesarean section for an abruptio placentae. Because of a prolonged and unprogressive labor, the patient was brought to the operating room for delivery by section. Twenty minutes before the operation the patient was given 1/150 gr. of atropine sulphate by hypodermic. Blood pressure at the start of operation was 120/90, pulse 76. The anesthetic agents used were ethylene and ether, administered by the closed, carbon dioxide absorption technique. At no time did the depth of anesthesia exceed that of first plane. A low cervical section was performed with the delivery of a living child. Immediately following delivery an ampoule of ergotrate was administered intramuscularly. Because of persistent poor uterine tone, 1 c.c. of obstetrical pituitrin was injected into the uterus; at this time the patient's blood pressure was 130/84 and pulse 100. Within five minutes the pulse rate rose to 120, while the blood pressure could not be obtained. The patient presented the picture of shock. For the following sixty minutes, the blood pressure could not be obtained. Ephedrine sulphate (gr. ¾) was given intramuscularly some thirty minutes after the appearance of shock with a resultant rise in pulse rate to 170-180 per minute with no effect on the arterial pressure. Pooled serum (500 c.c.) and 5 per cent glucose in saline (800 c.c.) were administered intravenously. Sixty minutes after the appearance of shock the systolic blood pressure could be obtained at 100, while the pulse rate fell to 140. The patient's recovery thereafter was rapid and uneventful. An intradermal skin test with obstetrical pituitrin (0.2 c.c. undiluted) resulted in the prompt appearance of a large urticarial wheal and a wide margin of erythema. On the fourth postoperative day the patient was given 500 c.c. of citrated blood because of profuse vaginal bleeding; this promptly produced a diffuse maculopapular eruption which was relieved with adrenalin.

Here, too, the absence of significant hemorrhage and surgical trauma and the almost immediate occurrence of shock on the injection of pituitrin point with certainty to the pituitrin as the responsible agent. The positive skin test and the maculopapular eruption following the transfusion indicate a state of allergy and suggest very strongly the possibility of anaphylaxis as the mechanism underlying the shock.

The remaining 5 cases of pituitrin shock occurred in women on whom vaginal hysterectomies were performed and who received intrauterine surgical pituitrin (1 to 2 c.c.) at the beginning of the operation. All recovered with no untoward effects. Of these 5 patients, only one was skin tested with pituitrin, and this one was found to be negative. These cases represent an incidence of 5 per cent of the total cases observed by the physician anesthetists.

MECHANISM OF PITUITRIN SHOCK

Various theories have been offered to explain the mechanism of pituitrin shock; these may be listed as (a) histamine reaction, (b) anaphylaxis, and (c) cardiac effect.

(a) In a discussion of our cases one may promptly dispose of the suggestion that histamine in the posterior pituitary preparation was the responsible agent, inasmuch as our solutions were histamine-free.[8] This does not exclude histamine as a cause of shock in the use of earlier posterior pituitary preparations which were admittedly less pure than those of today.

(b) That anaphylaxis may well reproduce the clinical pictures described is unquestioned. Most of the cases examined in the literature revealed, in addition to shock, the clinical features of urticaria, pruritus and angioneurotic edema. Where skin tests were performed, all revealed sensitivity to the posterior pituitary preparation. Many cases presented a history of having received a posterior pituitary preparation on some previous occasion. The studies of Simon and Ryder[9] would indicate that the responsible antigen was not the oxytocic or vasopressor fraction, but rather some other constituent of the gland. In this paper it will suffice to emphasize the possibility of pituitrin anaphylaxis.

(c) Of more interest to us are the cardiovascular effects of pituitrin, effects which have received too little attention by the clinician and merit some detailed discussion. It would appear paradoxical that a posterior pituitary preparation containing a pressor substance (pitressin), should produce shock by some mechanism other than anaphylaxis; however, the physiologic explanation is not lacking.

It is commonly held that the injection of a posterior pituitary preparation results in a rise in arterial pressure, but this is erroneous.

Moffat[10] found insignificant blood pressure changes in the unanesthetized patient following intramuscular administration of pituitrin. Woodbury and co-workers[11] observed transient falls in arterial pressure in anesthetized and unanesthetized patients following the intravenous and intrauterine administration of surgical and obstetric pituitrin; these falls were in the range of 30 to 50 mm. Hg. They also showed that the intravenous administration of three units pitressin produced very small rises in blood pressure.

Our own observations in anesthetized patients indicate that the intrauterine and intramuscular administration of surgical and obstetrical pituitrin are followed by variable results; there is usually no appreciable change, and infrequently, a significant rise or fall in arterial pressure.

In the experimental animal, the effects of pituitary preparations on blood pressure have been varied.

Gruber[12] demonstrated that pitressin in the unanesthetized dog produced a fall in arterial pressure when given intravenously; pitocin gave variable results while pituitrin produced a rise in pressure. These findings were confirmed by Melville.[13] In the anesthetized animal, Raginsky[14] obtained results dependent upon the anesthetic agent used; thus, with chloretone, pituitary extract produced almost constantly a rise in blood pressure; with ether the results were of a pressor, depressor, or mixed type; with luminal the effect was pronouncedly one of a depressor type. It is generally agreed that the pressor response to pituitrin is due to arteriolar and capillary constriction. The explanation for the fall in blood pressure is to be sought elsewhere in the cardiovascular system; here our attention is brought to the action of pituitrin upon the heart and coronary vessels.

It has been shown by Melville and Stehle[15] that the pitressin fraction possesses a potent constrictor effect upon the coronary arteries; this has been confirmed by Visscher[16] and Katz and co-workers.[17] Such coronary constriction leads to anoxia of the myocardium to a degree that will vary with the intensity and duration of the constriction. Grollman[18] suggests that pituitrin per se may interfere with the oxidative processes of the heart and thus augment the anoxic action of coronary constriction. It is of interest to note that Resnik and Geiling[19] point out the

similarity between the effects of anoxemia and of the injection of a posterior pituitary preparation on the heart. Goldenberg and Rothberger[20] stressed the similarity between the effects of pituitrin on the electrocardiogram and the electrocardiographic changes in angina pectoris and experimental coronary occlusion.

An anoxic heart will dilate; thus, Kolls and Geiling[21] demonstrated by fluoroscopy and teleoroentgenograms that pitressin produced dilatation of the heart. With a dilated, anoxic heart, there will result a reduction in cardiac output even to zero, with a resultant fall in blood pressure to an extent that will depend upon the degree and duration of the myocardial anoxia. The mechanism of pituitrin shock when not due to anaphylaxis is briefly as follows: coronary constriction, myocardial anoxia, dilatation of the heart, decrease in cardiac output, fall in blood pressure.

The role of the anesthetic agent in pituitrin shock is an uncertain and speculative one.

The most significant studies in this problem are those of Melville[22] who observed that dogs under sodium phenobarbital anesthesia were peculiarly sensitive to posterior pituitary extract as evidenced by the occurrence of ventricular fibrillation and death. Melville concluded that the coronary constriction in the phenobarbitalized dog was greater than in the unanesthetized dog and that this drug exerted some depressant action on the myocardium. From the work of Cattell,[23] it would appear that ether will enhance the action of pituitrin on the heart. He demonstrated an increase in heart volume during inhalation of ether, the heart volume steadily increasing with deepening anesthesia. In addition, Cattell showed that ether has a depressing effect on the blood pressure in shock, perhaps due to some disturbance in the vasoconstrictor system.

It is interesting to speculate that the inhibition in tissue oxidation under narcotics and anesthesia[24] is a factor that sensitizes the heart under anesthesia to the deleterious effects of pituitrin.

THERAPY

The treatment of pituitrin shock in the unanesthetized individual whether due to anaphylaxis or to coronary constriction, is the same: intravenous fluids, preferably blood or serum, oxygen and adrenalin or ephedrine. The use of adrenalin and ephedrine in anaphylaxis need not be expanded upon. However, it is well to point out the rationale of the use of these drugs in pituitrin shock due to coronary constriction. Melville and Stehle[15] have shown adrenalin and ephedrine to be effective antagonists of pituitrin by virtue of their dilating action on the coronary arteries.

In the anesthetized patient, the problem of therapy is less simple since the anesthetic agent may sensitize the heart to adrenalin and ephedrine, so that the use of either drug might prove catastrophic to the patient. Thus, Meek and co-workers[25] have shown that cyclopropane has a marked sensitizing effect upon the cardiac automatic tissues so that adrenalin may produce ventricular tachycardia or ventricular fibrillation; adrenalin is contraindicated in cyclopropane anesthesia. These same workers also found that adrenalin produced fast nodal tachycardias under ether anesthesia, an undesirable burden in an already anoxic heart in shock.

Orth and co-workers[26] found that cyclopropane and ether sensitized the sinoauricular node with the result that ephedrine will produce

greatly increased sinoauricular rates. In retrospect, the use of ephedrine in our second case of pituitrin shock, with a rise in ventricular rate from 120 to 180, probably demonstrated the production of an increased sinoauricular rhythm during ether anesthesia.

Orth and co-workers also observed that neosynephrin could be used safely under ether and cyclopropane anesthesia as an analeptic; if available, neosynephrin may therefore be used in conjunction with intravenous fluids and as much oxygen as maintenance of anesthesia permits.

There is no contraindication to the use of adrenalin or ephedrine under ethylene or nitrous oxide anesthesia.

DISCUSSION

The cases herein reported and those found in the literature serve well to indicate that pituitrin shock is no rare occurrence, and it is safe to say that its frequency is far greater than suspected and reported. Little consolation can be found because of the absence of case reports of deaths following the use of posterior pituitary extracts; too often such catastrophes are treated with complete silence.

It is the problem of the surgeon and the physician anesthetist to reduce the incidence of pituitrin shock to a minimum. The surgeon may help attain this end, first, by appreciating the pharmacologic effects of posterior pituitary extracts, and second, by defining clearly the indications for and the mode of use of such preparations. We have emphasized the former; some attention may well be paid the latter.

The use of pituitrin (intrauterine or intramuscular) to diminish bleeding during a vaginal or abdominal hysterectomy is a poor and dangerous substitute for careful and scrupulous hemostasis; the possibility of an intrauterine injection being made into a vein is great. Similarly, the intrauterine administration of pituitrin during a cesarean section is hazardous in view of the great vascularity of a gravid uterus. Where an oxytocic agent is needed, it would be more discrete to use an ergot preparation or pitocin which has no constrictor action on the coronary arteries. In addition, the obstetrician should be aware of the fact that sensitization to posterior pituitary preparations from previous administrations is not rare and should be alert to the possibility of an anaphylactic reaction.

When repeated injections of pituitrin are contemplated, as in postoperative abdominal distention, conservative doses should be the rule, averaging 10 to 20 pressor units for the individual dose; at this point reference may be made to a paper by Chaikoff[27] who advises that when pituitrin (or pitressin) is used in postoperative abdominal distention, it be combined with ephedrine, the latter in order to neutralize the coronary constriction of pituitrin.

The use of pituitrin as an analeptic in spinal anesthesia and shock is unsafe, carrying as it does the danger of coronary constriction; however, it may be effectively and safely used for such purposes when combined with ephedrine. This combination has been suggested by Melville[28] and its value confirmed by Hand and Sise[29] and Chaikoff.[27]

The use of pituitrin in patients with evidence of coronary insufficiency should be interdicted.[30] One of our patients was a middle-aged colored female with syphilitic heart disease. Surgical pituitrin (1 c.c.) was injected into the uterus against the advice of the medical anesthetist, with the prompt appearance of shock. Recovery was uneventful.

Finally, when the use of pituitrin is essential, care must be taken that it is not given intravenously—this by a simple aspiration test in two planes before injecting.

As for the physician anesthetist, it is not sufficient that he merely knows that pituitrin shock may occur under anesthesia. It is within his province to warn the surgeon of the effects of pituitrin and to express an opinion as to the advisability of its use. The administration of pituitrin during anesthesia should be guided by the anesthetist whenever possible, to insure that the preparation is not given intravenously. When pituitrin shock does occur under anesthesia, the course of therapy should be guided by the physician anesthetist who is in a position to judge best the behavior and state of the patient and the response to the various therapeutic procedures.

SUMMARY

1. Seven cases of pituitrin shock occurring under anesthesia are reported, two in detail. A brief review of the pertinent literature is presented.

2. Pituitrin shock may be a manifestation of (a) anaphylaxis, frequently due to previous sensitization with a posterior pituitary preparation, or (b) coronary artery constriction with resulting myocardial anoxia, cardiac dilatation, and decreased cardiac output.

3. Therapy in the unanesthetized patient, whether due to anaphylaxis or coronary constriction, should consist of adrenalin (or ephedrine), intravenous fluid, and oxygen. In the patient anesthetized with ether or cyclopropane, adrenalin (or ephedrine) might prove deleterious to the patient, and therapy should be confined to the use of intravenous fluid and oxygen.

4. Modes of usage of pituitrin are discussed with a view toward elimination of shock reaction.

The authors are indebted to Dr. Ralph Reis and Dr. Irving Stein for the privilege of reporting their cases.

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DISCUSSION

DR. HAROLD O. JONES.—We have used pituitrin, usually 1 c.c. of surgical, in many plastic vaginal operations as well as abdominal procedures. We have not appreciated many of the mild reactions as due to pituitrin but have interpreted them in terms of the surgical procedures performed.

Pituitrin has been of distinct value in reducing the blood loss during vaginal hysterectomy, and in our experience has not resulted in any instances of late hemorrhage.

In the patients under my own observation, we have had only one with appreciable "shock" quite certainly due to pituitrin. This patient was sent to the operating room for a diagnostic curettage on account of uterine bleeding; no anesthetic agent was administered, as it was found that the cervix was so patulous that dilatation was not necessary. Curettage was carried out and rather free bleeding followed. One cubic centimeter of surgical pituitrin was injected into the tissues at the side of the cervix; care was taken to be sure that the needle did not enter a vein. The patient returned to the ward in good condition and a few minutes later was in very profound shock, pulseless, cold and clammy, blood pressure 60/—, respirations 8 per minute. Intravenous fluids, ephedrine, oxygen caused some response, but not until twelve hours later did we feel safe about this patient. This patient recovered without any detectable residues. We did not test out her sensitivity to pituitrin later.

CANCER OF THE CERVIX FOLLOWING SUPRAVAGINAL HYSTERECTOMY*

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THERE is still a difference of opinion as to the advisability of doing a total hysterectomy in all cases if the uterus is to be removed as a prophylactic measure against a possible carcinoma developing in a retained cervix. In 1934 Von Graff wrote an article advocating that total hysterectomy should be done routinely. Since then several authorities have taken the opposite view in their discussions.

All will agree that the total operation offers the best protection from cancer, although cancer of the cicatrix in the vaginal vault occasionally occurs. Tyler has reported 13 cases of cancer of the vaginal vault following the total operation, and Rouhier reported an epithelioma of the cicatrix in the vaginal vault twenty-six years after total hysterectomy.

In these cases there naturally arises the question as to whether some portion of the cervix was left unintentionally, or was it a primary carcinoma of the vagina.

The technique employed in the complete operation should preserve the supporting structures of the upper pelvic floor. The technique described by Worrall of Australia and that of Lahey of Boston, if properly done, includes the entire portio vaginalis and is not difficult. In my experience it has been most satisfactory. Richardson and Farrar have also described efficient techniques.

However, many surgeons believe that there is a definite increase in the postoperative mortality and morbidity in the total operation as compared to the subtotal, and that the incidence of stump cancer is less than the increase in mortality percentage, especially where there is no disease or injury of the cervix. There is also a difference of opinion as to the cure rate obtainable in these stump cases. Prominent authorities have argued both sides of these questions.

In 1896 Chrobak first described, as a clinical entity, carcinoma of the stump of the cervix left after subtotal hysterectomy. Polak in 1921 collected 256 cases from the literature which awakened interest in the subject, and numerous reports of this condition continue to appear, especially during the last decade.

The incidence of stump cancer is difficult to determine and varies greatly in different reports. Von Graff found in one compilation of 7,244 subtotal hysterectomies there was an incidence of 45 stump cancers, or 0.62 per cent, while in his report of the number of stump cases found in a series of carcinoma of the cervix from different cancer clinics, there were 176 in 4,269, or 4.1 per cent. This is an approximate average percentage, although some clinics have a much higher incidence. In 1933 we reported 40 cases in 558, or 7.2 per cent.

Formerly 0.6 per cent was considered the probable incidence, while today 4 per cent is six and one-half times greater, and the real frequency may be still larger. The difficulty in determining the incidence

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is due to the uncertainty of the presence of carcinoma at the time of the subtotal operation. It is fair to presume that the carcinoma was already present if it appears within the first year after the subtotal hysterectomy.

Pearce of Boston stresses the slow development of carcinoma in some cases, mentioning as long as four years after its onset. Nuttall and Todd suggest a two-year criterion; Healy believes a three-year period should elapse as a fair index, to which Behney agrees.

It is important to note that there is a coincidence of fibroids and cancer in the same uterus.

Herbert Spencer, in 1902, was the first to recognize the frequent coincidence of malignant disease with fibroids. He found 4 cases of cancer in 200 fibroid uteri. Schottlaender found 12 in 600, and Noble found 2 in 100 cases, or a total series of 18 cancers in 900 fibroids, or 2 per cent. Labey, in 1924, before the French Congress of Surgery, stressed the frequent association of fibroma and cancer as proved by total hysterectomy. Piquand found in 600 uteri without fibroids 4 cases of cancer and in 600 cases with fibroids 21 cases of cancer. As most hysterectomies are done for fibroids, this is an important factor to consider in choosing the type of operation.

Spencer, Masson, Von Graff, Lynch, Sampson, Farrar, and many others advocate routine total hysterectomy as a prophylactic measure against stump cancer, believing that there is very little added risk in skilled hands.

Healy states the low incidence does not justify the total operation on account of increased mortality.

Scheffey, Behney and Meigs, among others, do not advocate the total operation in every case, reserving it for those in which the cervix is badly diseased. In the milder cases they advocate appropriate preliminary treatment, such as cauterization or repair.

Some surgeons rely on coning out the mucosa of the cervix, or cauterizing, or carbolizing its cavity as a preventive of malignancy. This is no safeguard, as 80 per cent of cancers originate on the portio vaginalis.

Sidall and Mack showed that in average hands the mortality of the total operation is higher than the subtotal. In 4,559 total operations, it was 3 per cent, and in 7,795 subtotal, it was 2.6 per cent.

Richardson expects the mortality in either operation should not exceed 1.5 per cent in skilled hands, but points out that in the total operation the morbidity and complications are greater, and that it is not the average operator alone who finds it more difficult.

Hochman, a student of mine, studied, under my supervision, 1,114 cases of total and subtotal hysterectomies and reached the conclusion that in the hands of the average operator there is a definite increased operative risk accompanying the complete operation.

In my experience, the incidence of vesicovaginal fistula is higher in stump carcinoma, probably due to the effect of the radium or the carcinoma on the bladder, which is in close approximation to the top of the stump. I have found it one and one-half times higher in these cases. Behney found fistula three times as often in treated and untreated stump cases of his series. Consequently, I believe it is wiser and safer to give divided doses of radium rather than one large dose.

The difficulty in applying the radium varies according to the extent of the disease and the shape and size of the cervix. Behney's method of splitting the cervix transversely with the radioknife to allow of the

insertion of the radium capsule is a great help in some cases. In our cases we place a radium capsule in the cavity of the cervix, 50 or 100 mg., and implant platinum needles, 12½ mg., 4 to 6, in the periphery according to the size of the cervix, giving an average dose of 3,200 to 3,600 mg. hours, which may be divided as indicated. This is either preceded or followed by high voltage x-ray therapy, preferably by the Coutard technique. Fricke of the Mayo Clinic gives up to 4,000 mg. hours in 3 or 4 divided doses, plus x-ray.

The opinion as to whether the total removal has a higher mortality rate than the subtotal operation varies in accordance with the experience of the surgeon. Many only remove the cervix when it is easy to do. The skilled operator will no doubt have less difficulty than the occasional surgeon. There is no question, however, that some cases, are extremely difficult for any surgeon on account of obesity, adhesions, and fixation of the uterus. The total removal in such cases is a more severe procedure, no matter who does it or by what technique, and the mortality and morbidity will average higher.

In my opinion, in view of the rate of incidence as we see it, and the more frequent association of carcinoma with fibroma, it is best to remove the entire uterus in all cases where there is no probability of serious increased risk. If the cervix is retained on this account, it should be coagulated or repaired when indicated, and meticulously watched in a careful follow-up over an extended period of time. Whenever a hysterectomy is contemplated, the cervix should always be carefully studied, and if suspicious a biopsy should be made.

It is important that the uteri removed be opened and inspected at the time of operation, and if the cervix is suspicious it should be removed in spite of an increased risk.

RESULTS

Healy and Arneson in 1935 published their results obtained in treating stump cancer, and their five-year salvage was 14 per cent. They attributed their poor salvage to the anatomic difficulties and change caused by the absence of the fundus, as it did not allow of the same perfect application of the radium, or the same degree of dosage. The 14 per cent was lower than their salvage percentage of all their cancer cases. They state, however, that their results in the advanced cases of stump cancer equaled their results in advanced cancer with the uterus present. They evidently rely more on the external radiation with x-ray, advising the Coutard technique.

On the other hand, Behney has reported a 10 per cent better percentage in his stump cases than in his total series; and Scheffey's salvage was 42.8 per cent against 20.5 per cent for his total cases.

The last report from the Woman's Hospital on carcinoma of the stump was published three years ago when Dr. Sackett found an incidence of 7.2 per cent. This report included all cases, even though they occurred within the first year following hysterectomy. I have recently had the records brought up to date, from May, 1919, to November, 1940. This shows that in 879 patients with carcinoma of the cervix there were 61 stump cases, or 6.9 per cent. In 49 observed during a five-year period, 21 were living, or an absolute survival rate of 42.8 per cent; and in 20 observed during a ten-year period, 10, or 50 per cent, were living. Our five-year salvage of all cancer of the cervix cases was 28.5 per cent. In the 61 cases, 16 were within the first year after operation. Of these, 5 survived five years and 3 ten years. Undoubtedly the disease was already present in some of this group at the time of the hysterectomy.

In 41 the disease developed more than one year after operation. Sixteen of this group survived five years, or 32.7 per cent of 49 observed, and 7 survived ten years, or 35 per cent of 20 observed.

There were 32 cases arising three years following operation, or 3.64 per cent, which approaches the 4 per cent of average incidence in which the carcinoma was not present at the time of hysterectomy.

In the 61 cases, the extent of the disease was classed as early in 16 and advanced in 45. Forty-seven cases were squamous cell carcinoma, of which 20, or 44 per cent, survived five years, and 9, or 20 per cent, survived ten years. There were 12 patients with adenocarcinoma, 2, or 20 per cent, surviving five years, and 1, or 10 per cent, ten years. In 2 cases the type of cell was undefined. The incidence of fistula was one and one-half times as high in our stump cases.

The average dose of radium applied was approximately 3,200 mg. hours of element. High voltage x-ray follows, or precedes, preferably after the Coutard technique. Before 1930 we had no high voltage x-ray. Thirty-six patients were treated with radium alone (of these 29 were under treatment before 1930), 16 of these survived five years, and 9 survived ten years. Twenty-four patients were treated with both radium and x-ray; of these, 5 survived five years and 1 survived ten years. One patient was not treated.

As Behney has pointed out, the salvage of stump cases for five years in Scheffey's, Behney's, and our Clinic, if combined, was approximately twice that achieved with general carcinoma of the cervix in the same Clinics.

COMMENT

The general impression has been that cancer of the stump is more serious and more difficult to treat, with less hope of success than cancer of the cervix with the fundus present. With the exception of the increased frequency of fistula, which may be due to the carcinoma as well as the radium, in view of our results and those obtained by Scheffey, Behney, and others, I do not believe the above statement is justified. I agree with Behney's statement in a recent paper before the American Gynecological Society that stump cancer behaves and responds to treatment in a manner similar to cases where no operation has been done, with generally better results. If castration is combined with the subtotal hysterectomy, it should be expected to be a retarding factor in the cancer development due to diminished circulation and lymphatic drainage.

In my opinion the total operation is to be preferred and is my present practice, because of the evident higher incidence of stump cancer than was formerly thought to occur, and of the frequent association of cancer with fibroids. Yet we must recognize that in average hands there is more danger of a higher mortality, and such complications as injury to the bladder and ureters, infection, and lack of vaginal support than in skilled hands. Also the expert surgeon will meet cases with a definite increase in risk due to obesity, adhesions, fixation, or systemic disease, which makes the subtotal operation a safer and wiser procedure. If, however, the subtotal operation is considered, a careful study of the cervix should be made and appropriate treatment used if indicated.

In all subtotal operations, the possibility of cancer should be borne in mind, and a careful follow-up for an extended period of time is essential for safety.

101 East Eightieth Street

SOME CLINICAL OBSERVATIONS ON THE ENDOCRINOLOGY OF ABORTION*

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THE etiology of abortion is varied. When no medical or gynecologic cause is apparent, it has been common practice to look for some disturbance in the endocrine system or to take ultimate refuge in some theory of glandular failure. At times, clear-cut factual data are available to establish the endocrinopathy of abortion. The high incidence of abortion in hypothyroid women and the specific therapeutic efficacy of thyroid substance are well known. Abortion is a common complication of pregnancy in diabetic women, the incidence of which has not been altered significantly by adequate therapy with insulin and diet. Myopathic insufficiency of hypoplastic uteri, resulting from embryologic faults or from adolescent ovarian failure, may cause abortion. The most common theory employed to explain repeated abortions, when no organic or traumatic factors exist, is based on an assumed intercurrent ovarian or placental failure. This communication deals with some clinical observations pertinent to this theory.

A time-honored concept of the physiology of corpus luteum attributes to it the role of protecting and nurturing the product of conception. Its active principle, progestin, has been described as exerting a quieting and relaxing action upon uterine musculature. Accepted as generally as it is in experimental biology, this concept has both its ardent proponents and opponents in clinical endocrine gynecology. Falls and his co-workers[1] regard progesterone as a quantitative, biologic antidote to pituitary oxytocin, endogenous and exogenous. Kurzrok and his associates,[2] on the other hand, have observed increased uterine contractility following injections of progesterone.

Further considerations indicate that, despite the fundamental role attributed to it in the physiology of pregnancy, the corpus luteum at times is not indispensable to the normal progress of gestation. Pratt[3] reported in 1927 the nonoccurrence of any interference with the course of pregnancy or lactation in the instances of 2 women whose corpora lutea were removed during the first month of pregnancy, in fact prior to the first missed period. Such observations may even cast doubt upon the absolute necessity for the corpus luteum in implantation of the fertilized ovum. Ask-Upmark[4] reviewed the records of 51 women from whom the corpora lutea were removed during the first two months of pregnancy. Pregnancies continued in 9 of these women, despite the fact that in 4 instances corpora lutea had been removed during the first

*Read, by invitation, at the Detroit meeting of the Michigan Society of Obstetricians and Gynecologists, October 1, 1940.

month of pregnancy. On the other hand, there is a mass of surgical data which indicate that trauma to, or removal of, the corpus luteum in the early months of pregnancy commonly results in abortion. There is, however, general acceptance of the belief that corpora lutea or even both ovaries may be sacrificed during the later stages of pregnancy with no untoward sequelae as regards the course of pregnancy. Explanation of this dispensability of the corpus luteum rests upon the assumption that its endocrine functions are taken over by the chorioplacental system.

A definite division of labor, as regards endocrine function, between the ovaries and the chorioplacental system has been envisioned by Browne and Venning.[5]

They divide pregnancy into ovarian and chorioplacental phases. During the ovarian phase the urinary excretionary values of estrogens and of the pregnanediol complex are low, while those of the gonadotropins are high. During the chorioplacental phase these values of estrogens and pregnanediol complex increase, while those of gonadotropins decrease. The time of transfer of endocrine responsibility from the ovaries to the chorioplacental system is said to vary markedly and to be indicated roughly by a peak in the urinary excretion of gonadotropins. This theory assumes that an early transfer of responsibility to the chorioplacental system may permit early sacrifice of the ovaries. In such striking instances of dispensability of the corpus luteum as reported by Pratt, one may assume that an essentially normal progestational endometrium may be capable of supplying the hormonal requirements for the continuation of pregnancy.

There is an abundance of data to confirm the belief that the chorioplacental system is a source of the hormonal plethora of pregnancy.

Allan and Dodds[6] summarized 4 histories of patients reported by Amati, Szarka, Waldstein, and Saidl and added one patient of their own in whom pregnancy continued despite bilateral oophorectomies. They observed in the records of these patients no significant alterations in the urinary excretionary values of gonadotropins, but they did observe definite decreases but no absences of estrogens. Venning and Browne observed no significant alterations in the urinary excretion of estrogens and of pregnanediol complex in a patient in whom pregnancy continued despite the removal of the corpus luteum on approximately the ninetieth day of pregnancy.

Studies of functional levels of corpus luteum activity in abortion as well as in other conditions related to ovarian failure have been hampered by the fact that biologically active progestin either does not occur or occurs in small quantities in the various fluids and tissues of the body.

Only small amounts of progestin were found by Adler and co-workers[7] and by Ehrhardt[8] in human placentas and in the urines of pregnant women. Loewe and Voss[9] found only 1 rabbit unit of biologically active progestin in 20 liters of urine from women during the last five days of the menstrual cycle. Bloch[10] reported that 500 c.c. of blood from a pregnant woman gave negative results when tested by methods of bio-assay. Clauberg and his associates[11] obtained only a questionable progestational reaction with an extract prepared from approximately 50 Gm. of human corpora lutea. Pratt and his co-workers,[12] however, were able to get positive tests in the immature rabbit with extracts equivalent to 60 Gm. of human corpora lutea. Our group[13] has shown that even after injections of rather large amounts of progesterone or after the ingestion of rather large doses of anhydrohydroxyprogesterone no biologically active progestin may be recovered from the urine.

Venning and Browne, however, in their various studies have been able to adapt Venning's method for the gravimetric determination of sodium pregnanediol glucuronide[14] to the study of progestin metabolism. They have submitted data to prove that pregnanediol is the major metabolic product of progestin. A number

of studies upon pregnanediol titers in health and disease has appeared. Stover and Pratt[15] observed no significant alteration in pregnanediol titers of 3 individuals who had signs and symptoms of threatened abortion (1 gave a history of repeated abortion). Buxton[16] recently reported the occurrence of normal titers of sodium pregnanediol glucuronide in the early pregnancies of 5 women, each of whom had 3 or more spontaneous abortions. Pratt and Stover and our group[17] reported simultaneously that injections of progestin or progesterone failed to increase pregnanediol titers of patients receiving this type of therapy. Further studies by our group[18] on the metabolism and utilization of crystalline progesterone continue to confirm these observations. It was found that quite large quantities of progesterone could be given without any pregnanediol being recovered from the urine. We also reported data which indicated that the injection of crystalline progesterone tended to inhibit the metabolism of the intrinsic progestin, i.e., pregnanediol titers were actually decreased by injections of progesterone. It was observed in these studies, however, that the concomitant administration of estrogens and progesterone tended to prevent this depression and at times resulted in some increase in pregnanediol titers. The simultaneous administrations of chorionic gonadotropins, progesterone, and estrogens yielded our only definite increases in pregnanediol titers. These observations seemed to cast considerable doubt upon the therapeutic specificity of progesterone in the treatment of threatened or habitual abortion, even in those instances in which low pregnanediol titers were associated. The theory of Browne and Venning that one might be able to establish quantitatively the progestin deficits by their method and to complement these deficits by progesterone therapy seems untenable.

CLINICAL DATA AND CASE REPORTS

The case records of 6 women who either had had repeated abortions or who were threatening to abort are reported. These patients were investigated both from an endocrine and a gynecologic standpoint. All had repeated daily determinations of pregnanediol by Venning's method. A number had daily determinations of 17-ketosteroids (products of androgenic metabolism) by Oesting's method.[19] All of these patients except one were treated with progesterone alone or with progesterone and estrogens, or progesterone and chorionic gonadotropins.

CASE 1.—Abortion at 6 months. No treatment except thyroid substance. A. B., colored, aged 35 years, married, para 9-9-0, was seen in the Endocrine Division Sept. 21, 1939, at which time she was approximately four months pregnant. All of her nine previous pregnancies had ended in miscarriages at five to six months of gestation. Endocrine and gynecologic surveys indicated no apparent abnormalities or disease except generalized obesity (weight 183 pounds). Roentgenogram of the sella turcica was normal. Basal metabolic rate was reported to be −20 per cent. The urinary excretion of sodium pregnanediol glucuronide was investigated from Sept. 22 to Nov. 6, 1939, i.e., to within five days of the time the patient miscarried.

These findings are presented graphically in Fig. 1. No treatment was given except thyroid substance to clinical tolerance.

The patient is now (Sept. 25, 1940) about five and one-half months pregnant and has been receiving anhydrohydroxyprogesterone,* 60 mg. a day, and thyroid substance to tolerance since the second month of pregnancy.

The abortion of this patient occurred at about the sixth month just as her previous 9 abortions. The pregnanediol titers were quite normal and compatible with the stage of gestation until a distinct fall in these occurred about a week before abortion. By referring to these titers, impending abortion could not have been diagnosed until the week before it actually occurred, and any treatment which had been anticipated upon the basis of low pregnanediol titers would not have been initiated until that time.

*Pranone, supplied generously by Schering Corporation, Bloomfield, N. J.

CASE 2.—Pregnancy successfully carried to term in a woman who had had 3 previous abortions. Treatment with progesterone and thyroid substance. Mrs. A. H., aged 26 years, para 3-3-0, was seen first in the Endocrine Division March 9, 1938, at which time she was about two and one-half months advanced in her fourth pregnancy. Her three previous pregnancies had been aborted spontaneously at about the third month. Gynecologic and endocrine surveys showed no evidence of endocrine disease, except symmetrical obesity and clinical hypothyroidism. A basal metabolic test done just prior to the beginning of pregnancy was reported as –21 per cent. This finding had resulted in the administration of thyroid substance to clinical tolerance throughout the course of the patient's pregnancy.

Fig. 2 indicates the course of this patient during her pregnancy up until delivery of a healthy child Sept. 24, 1938. During the pregnancy the patient received progesterone as indicated in the clinical chart and excreted rather normal amounts of sodium pregnanediol glucuronide.

One is inclined to attribute the successful outcome of this pregnancy to the thyroid substance given and to restricted activity rather than to the small dosage of progesterone, i.e., 1 mg. three times a week. Throughout pregnancy the patient's pregnanediol titers were essentially normal. The amount of progesterone given could not have maintained normal levels of pregnanediol excretion had these been significantly low initially. The patient's pregnancy was complicated by a moderate toxemia during the last month. The albuminuria during this time interfered with pregnanediol determinations which otherwise would have been continued until the onset of labor.

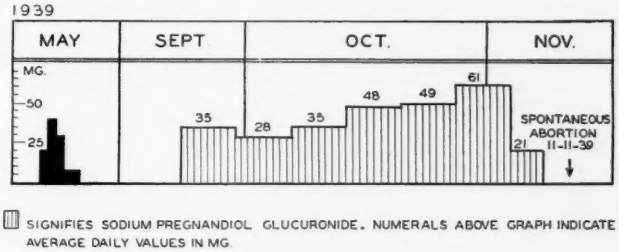

Fig. 1.—Case 1. Graphic clinical record, including urinary excretionary values of pregnanediol complex.

CASE 3.—Pregnancy following gonadotropic therapy in a patient with ovarian sterility. Threatened abortion during the third month of pregnancy, despite initiation of therapy with estriol glucuronide, progesterone, and chorionic gonadotropins as soon as pregnancy was diagnosed. Eventual delivery at term. Mrs. M. McC., aged 25 years, para 0-0-0, was seen in the Endocrine Division July 11, 1939, because of inability to conceive during her five and one-half years of marriage. She had received no endocrine investigation or therapy. Her last sterility investigation had embraced a tubal insufflation about two and one-half years previously. Despite the fact that she gave a history of marked oligomenorrhea since menarche at 15 until approximately one and one-half years previously, endocrine and gynecologic surveys were essentially normal. Roentgenogram of the skull was negative. Basal metabolism was –12 per cent.

The endocrine investigation of this patient, as well as the patient's therapy which resulted in pregnancy, and the course of this pregnancy, which was threatened by abortion, are given in Fig. 3.

The interest in this case lies in the fact that for an entire month this patient threatened to abort despite bed rest and despite prophylactic therapy designed to prevent possible abortion started when pregnancy was diagnosed. The patient bled so profusely during her threatened abortion that her obstetrician felt sure that she had aborted. Despite these symptoms of threatened abortion pregnanediol titers were increasing steadily and normally, and at no time were there observed any

critical depressions of these titers. The patient's therapy was continued through the eighth month of pregnancy. Whatever the cause of the patient's threatened abortion, it was not related to any depression in pregnanediol titers.

CASE 4.—Abortion at five and one-half months occurring in a patient who had had 3 previous abortions. Treatment with estriol glucuronide, progesterone, and chorionic gonadotropins. Mrs. R. M., aged 30 years, para 2-2-0, was seen first in the Endocrine Division Sept. 22, 1939, at which time she was in the process of having a six weeks' abortion. The patient aborted despite progesterone therapy three days later.

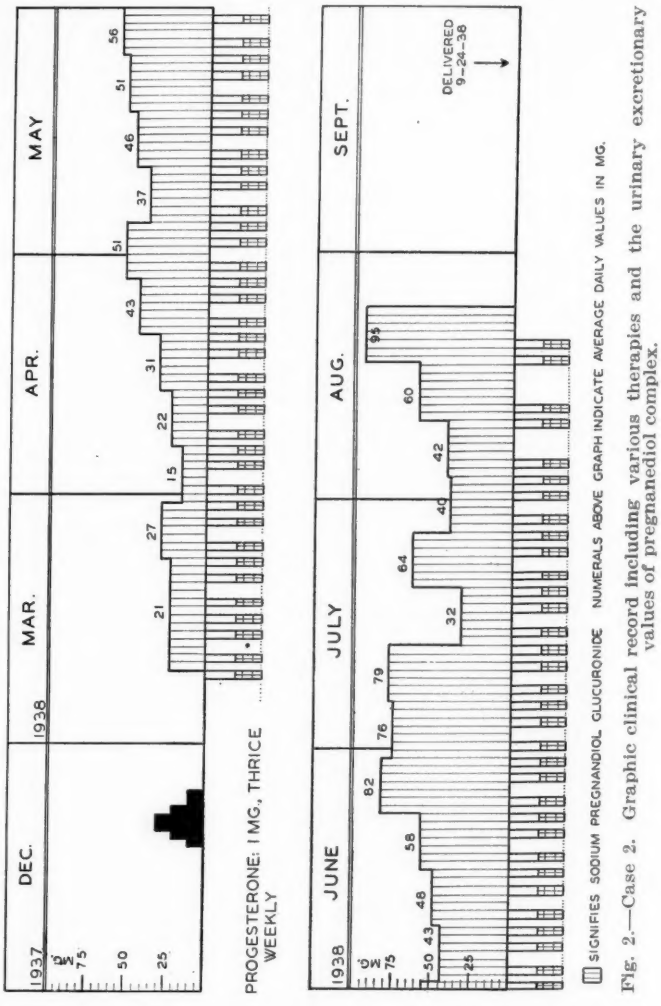

Fig. 2.—Case 2. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex.

The patient's two previous pregnancies had been aborted at about six weeks of gestation. General endocrine and gynecologic surveys showed no abnormalities. Basal metabolism was reported as −20 per cent.

Fig. 4 outlines the clinical course of the patient from the time of her third abortion through the beginning of her fourth pregnancy and until her fourth abortion. The patient received progesterone, estriol glucuronide, and chorionic gonadotropins as indicated in the clinical chart, as well as thyroid substance to tolerance.

The normal pregnanediol titers of this patient led to the hope that pregnancy would be carried to term. These titers during the three months they were investigated

showed a gradual and continual rise. Treatment was started as soon as her first period was missed and certainly must be judged to have been adequate. It was our feeling that since the patient carried this pregnancy so much longer than her 3 previous six weeks' abortions and since her pregnanediol titers were quite normal, she might have gone to term had not the premature rupture of membranes occurred. What success therapy attained in this case may well have been due to the thyroid substance rather than to the other agents used.

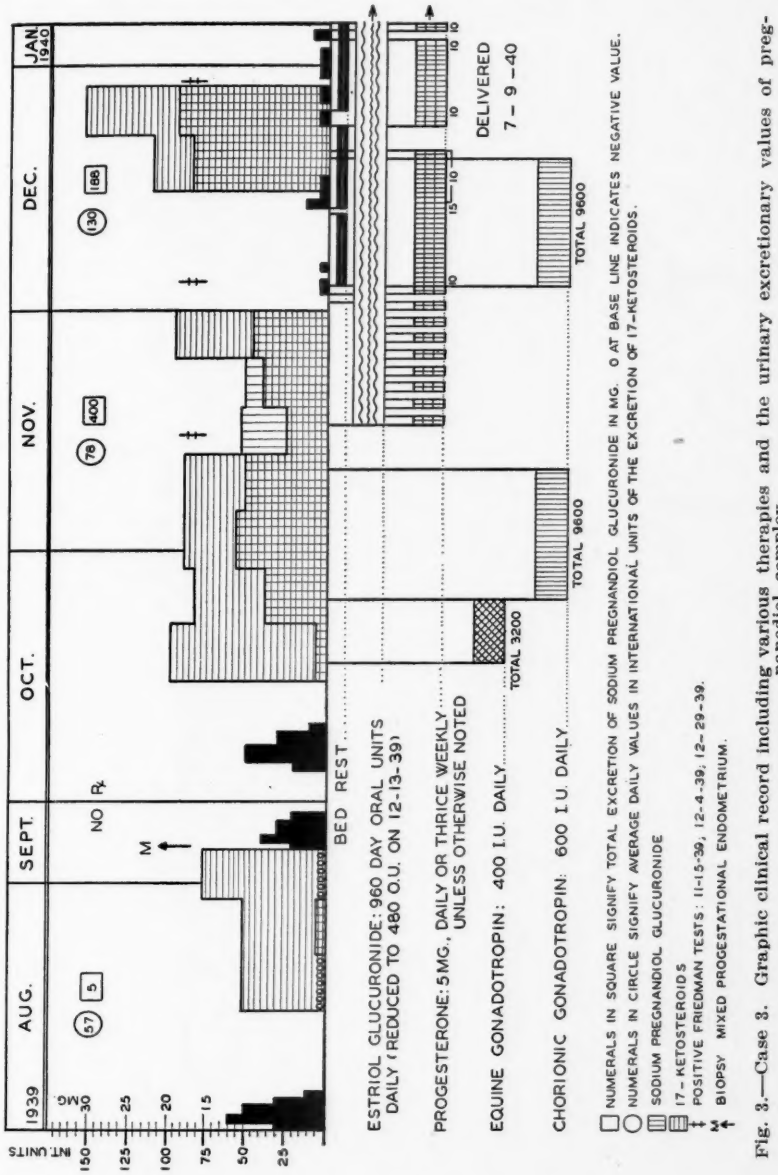
1939
AUG.
SEPT.
OCT.
NOV.
DEC.
JAN 1940
INT. UNITS
MG.
NO Rx
M
BED REST
ESTRIOL GLUCURONIDE: 960 DAY ORAL UNITS DAILY (REDUCED TO 480 O.U. ON 12-13-39)
PROGESTERONE: 5 MG., DAILY OR THRICE WEEKLY UNLESS OTHERWISE NOTED
EQUINE GONADOTROPIN: 400 I.U. DAILY
TOTAL 3200
CHORIONIC GONADOTROPIN: 600 I.U. DAILY
TOTAL 9600
TOTAL 9600
DELIVERED 7-9-40
NUMERALS IN SQUARE SIGNIFY TOTAL EXCRETION OF SODIUM PREGNANDIOL GLUCURONIDE IN MG. 0 AT BASE LINE INDICATES NEGATIVE VALUE.
NUMERALS IN CIRCLE SIGNIFY AVERAGE DAILY VALUES IN INTERNATIONAL UNITS OF THE EXCRETION OF 17-KETOSTEROIDS.
SODIUM PREGNANDIOL GLUCURONIDE
17-KETOSTEROIDS
POSITIVE FRIEDMAN TESTS: 11-15-39, 12-4-39, 12-29-39.
BIOPSY MIXED PROGESTATIONAL ENDOMETRIUM.

Fig. 3.—Case 3. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex.

CASE 5.—Miscarriage at seven months in a patient who had had 3 previous miscarriages or abortions. Treatment with progesterone and chorionic gonadotropins. Mrs. E. W., aged 26 years, para 3-3-0, was referred to the Endocrine Division Jan. 13, 1940, because of a history of three previous abortions or miscarriages. Gyneco-

logic and endocrine surveys indicated no significant disease. Basal metabolic rate was reported as +10 per cent, satisfactory. Roentgenogram of the sella turcica was normal. The details of the investigative studies done and of the patient's therapy during the course of her pregnancy are given in Fig. 5.

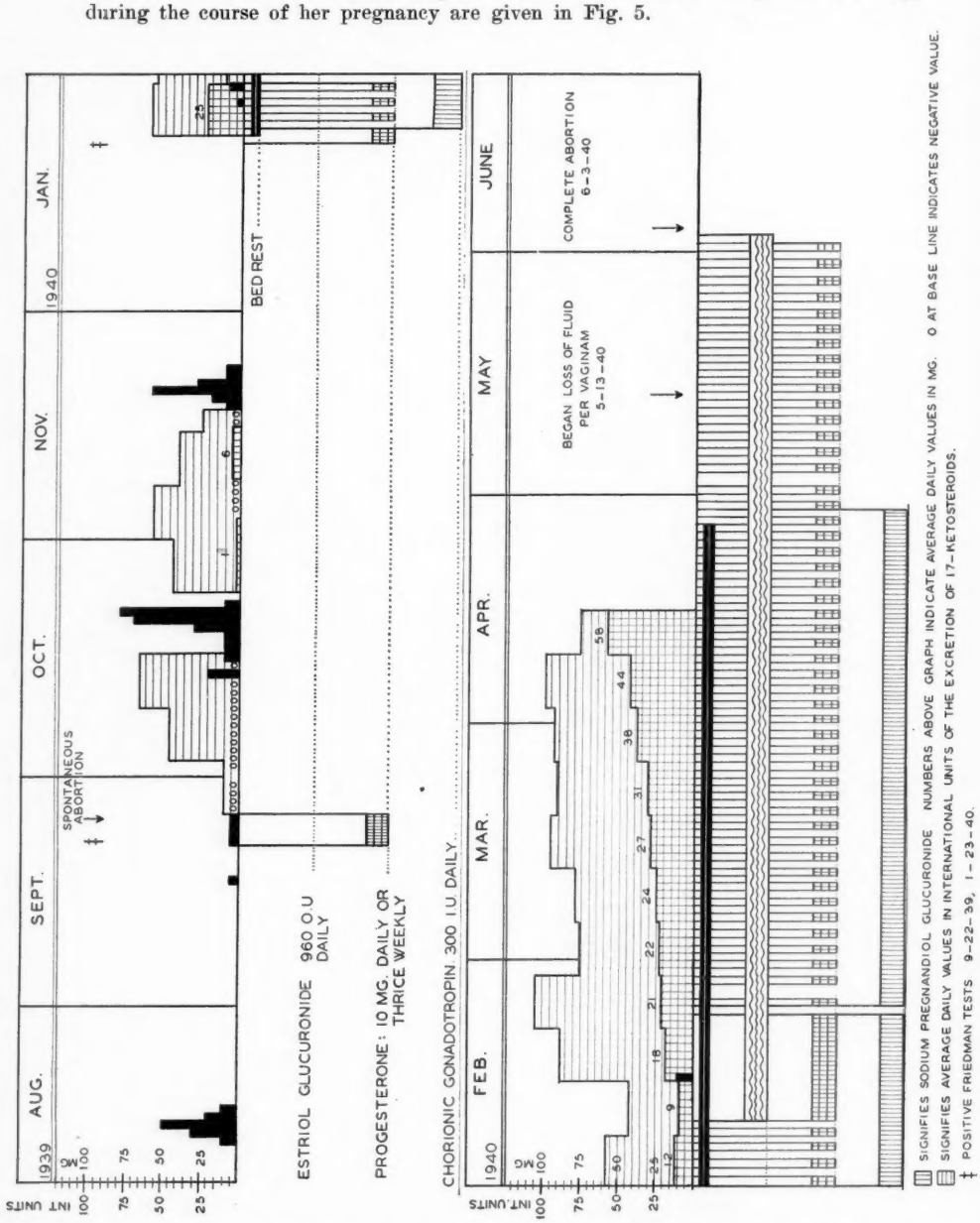

Fig. 4.—Case 4. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex.

On August 23 the patient reported that she had felt no fetal movements for two days. In view of this apparent fetal death and in view of low urinary titers of pregnanediol complex, therapy was discontinued. On August 26 the patient went into premature labor and delivered a macerated fetus of some seven months' gesta-

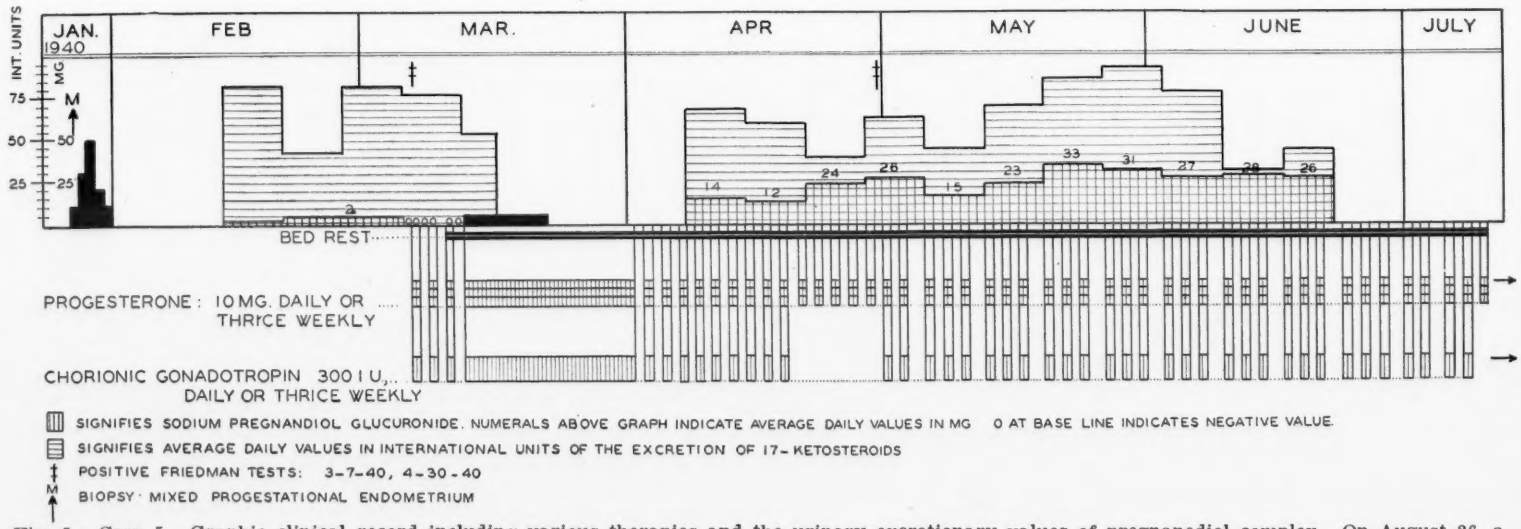

Fig. 5.—Case 5. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex. On August 26, a macerated seven months' fetus was delivered.

tion. The placenta was described by the pathologist as being full size with no gross pathologic changes. Microscopic examination likewise revealed no pathologic changes.

Abortion or miscarriage was anticipated from the early stages of pregnancy in this case because of the consistently low pregnanediol titers and because of the fact that even during her third and fourth month of pregnancy they had shown no substantial elevations; as a matter of fact these had started declining during the latter part of the third month. A striking finding was the extremely low values for pregnanediol during the menstrual cycle during which pregnancy occurred. For ten consecutive days during the progestational phase of this cycle, no pregnanediol was excreted, despite the fact that the patient was receiving both progesterone and chorionic gonadotropins.

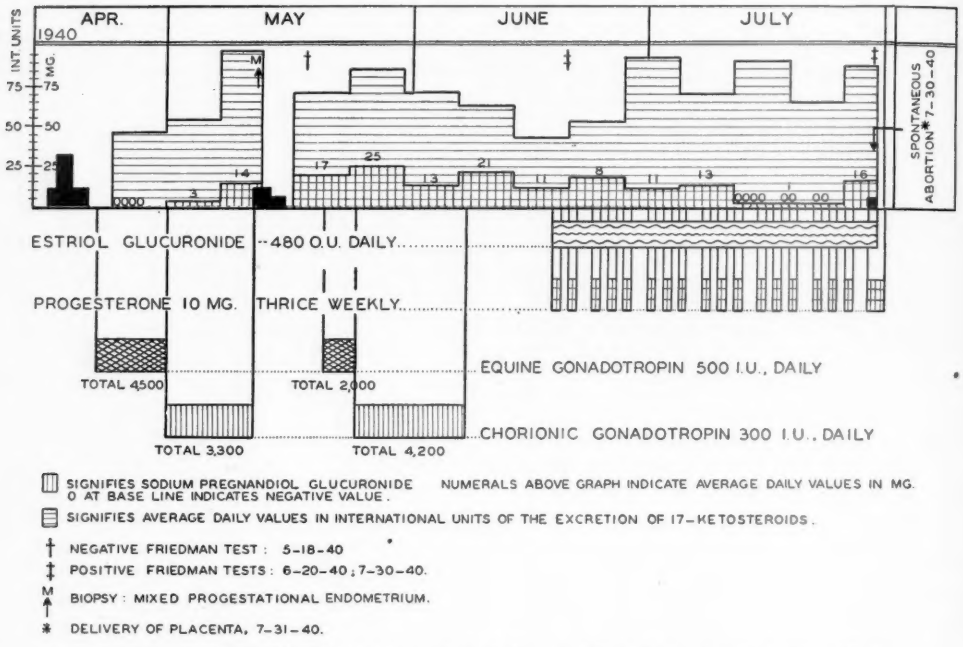

Fig. 6.—Case 6. Graphic clinical record including various therapies and the urinary excretionary values of pregnanediol complex.

CASE 6.—Abortion at three and one-half months by a patient who had had 3 previous abortions. Treatment with estriol glucuronide and progesterone. Mrs. L. R., aged 33 years, para 3-3-0, was first seen in the Endocrine Division Sept. 2, 1937. During the patient's previous five years of marriage 3 abortions had occurred at approximately the third month of gestation. Endocrine and gynecologic surveys were essentially negative except for clinical hypothyroidism. The patient's basal metabolic reading when seen first was −21 per cent. During a two-and-one-half-year period of observation and study no pregnancy occurred, despite the fact that metabolic irregularities were adjusted by thyroid substance to full clinical tolerance. These studies embraced quantitation of pregnanediol complex during 4 menstrual cycles with negative results and examinations of a number of endometrial specimens taken at onsets of episodes of bleeding. All of the latter showed estrogenic or minimal progestational responses.

On April 22, 1940, a series of cyclic gonadotropic therapy was instituted which led to a pregnancy. Fig. 6 presents graphically the clinical record from this time on, including therapy, urinary titrations for 17-ketosteroids, and sodium pregnanediol glucuronide. This record covers the cycle preceding pregnancy, the pregnancy, and

the patient's spontaneous abortion July 30, 1940. Gross and microscopic examinations of the placenta showed no abnormalities.

Abortion was anticipated in this case during the last six weeks of pregnancy because of the declining pregnanediol titers. There was a period of time just prior to abortion when the patient, despite treatment, excreted no pregnanediol for eight consecutive days; however, during the four days immediately preceding abortion, the patient excreted 16 mg. of pregnanediol and on the day of abortion gave a positive pregnancy test.

A complicating factor was introduced inadvertently in this case due to the fact that an endometrial biopsy was taken apparently at the onset of an episode of bleeding, which subsequently proved to have been most likely of implantational nature. No chorionic tissue was encountered in the endometrium secured at this time. The scantiness of this episode of flowing, the failure of the pregnanediol complex to disappear from the urine after this bleeding ceased, and the increased quantities of it excreted at this time seemed indicative of pregnancy, despite the negative pregnancy test. In 4 other similar instances, accidental biopsies at the time of implantational bleeding or during the first few weeks of pregnancy have been done; in only one of these did abortion occur, and here apparently the entire product of conception was removed during the biopsy. The other 3 patients who had biopsies at this time continued normally to term and delivered healthy babies. The facts that a positive pregnancy test was received the day of abortion, that no pathologic findings were encountered in the placenta, that no symptoms of impending abortion existed until a few hours before the abortion actually occurred, and that low urinary excretionary values of pregnanediol had characterized the last six weeks of pregnancy seem to relate the abortion to endocrine rather than to traumatic factors.

This case suggests two significant observations in regard to the hormonology of pregnancy. Significant increases of pregnanediol complex may be recognized in the urine during early pregnancy even prior to the excretion of sufficient concentrations of gonadotropins to yield a positive pregnancy test. Failure of the placental function of progestin-pregnanediol metabolism may occur prior to, and independently of, any significant alterations in gonadotropic output.

DISCUSSION

Studies of urinary titers of the pregnanediol complex yield equivocal data regarding the hormonology of women giving histories of repeated abortions. In some cases low titers may be encountered throughout the greater part of the pregnancy. In others, a critical fall in these titers does not occur until shortly before actual abortion. Abortion may threaten and, perhaps, may occur when the pregnanediol titers are normal (Case 3).

Our observations have indicated that when abnormally low pregnanediol titers are encountered, intensive therapy, even when initiated as soon as pregnancy is diagnosed, is unable to restore normal excretionary values or to prevent abortion. This is true of various combinations of therapy: Progesterone intramuscularly in oil in daily or thrice weekly doses varying from 5 to 10 mg.; similar amounts of progesterone combined with estrogens or with estrogens and chorionic gonadotropins (during first three to four months of pregnancy). The failure of this latter combination of therapy to prevent abortion in the patients in Cases 4, 5, and 6 warrants analysis. These 3 patients had varying grades of hypothyroidism and received in addition to the therapy mentioned, thyroid substance to full clinical tolerance. Had thyroid substance alone been given, better results would have been expected than those obtained.

It does not seem unlikely that the sterol and chorionic gonadotropic therapy given these patients may have interfered with the usual therapeutic efficacy of thyroid therapy.

The failure of even the large amounts of progesterone employed to increase the pregnanediol output of these patients agrees well with other reported studies of our group in nonpregnant women. At times during these studies, it was observed that the total output of pregnanediol was considerably less than that to be anticipated from the efficient metabolism of the injected progesterone alone. We are inclined, therefore, to believe that intensive progesterone therapy may actually lower the pregnanediol output of patients, i.e., decrease their intrinsic progestin metabolism.

Our observations warrant the belief that studies of urinary titers of the pregnanediol complex are of no clinical value in the diagnosis or treatment of impending or habitual abortion. They likewise indicate that, when low pregnanediol titers are diagnosed, the administration of amounts of progesterone theoretically capable of complementing the calculated pregnanediol deficit fails to effect any significant elevation in these titers.

SUMMARY

Some concepts of the hormonology of abortion have been reviewed and studies of progestin metabolism in patients with histories of repeated abortions have been reported.

The following observations seem warranted from our studies:

1. As a rule, pregnanediol titers tend to fall prior to abortion. This fall may be abrupt or gradual.
2. During the course of pregnancy prior to the onset of abortion titers may be normal or low.
3. Patients may threaten to abort when pregnanediol titers are normal.
4. Intensive therapy with progesterone, alone or combined with estrogens and chorionic gonadotropins, fails to elevate low pregnanediol titers and to prevent abortion.
5. There is a likelihood that large doses of progesterone may precipitate abortion by depressing the metabolism of intrinsic progestin.
6. Progesterone therapy may interfere with the therapeutic efficacy of thyroid substance in preventing abortion in hypothyroidism.
7. Any beneficial effect which therapy with progesterone possesses in the treatment of habitual abortion cannot be explained upon the basis of its complementing deficits in progestin-pregnanediol metabolism.

The progesterone used in these studies was supplied generously by the following concerns: Ciba Pharmaceutical Products, Inc., Summit, N. J. (lutocylin); Eli Lilly & Company, Indianapolis, Ind. (progestin); Schering Corporation, Bloomfield, N. J. (proluton). The chorionic gonadotropins (APL) and the estriol glucuronide (emmenin) were supplied by Ayerst, McKenna & Harrison, Montreal, Canada.

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THE EFFECT OF PREGNANCY ON EXPERIMENTALLY PRODUCED RENAL INJURY

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INTRODUCTION

THE tendency to associate the hypertensive syndromes in pregnancy with injury to the kidney has resulted from observations that water retention becomes obvious early in the disease,[1] that albuminuria is almost always present, and that nitrogen retention, although inconstant and later in appearance, is of frequent enough occurrence to point toward the renal system.[2] This view has been further strengthened by the demonstration that certain types of renal injury may cause transient hypertension,[3-5] that permanent elevations of blood pressure accompany reduction of the renal blood flow,[6] and that reduction of renal blood flow in the experimental animal causes a syndrome which closely resembles "eclampsia" in the human being.[7, 8]

The production of renal injury in the experimental animal has been thoroughly investigated and many different types of nephrotoxic substances have been used.[9] It is of interest, however, that only a few of these agents produce a noticeable degree of hypertension and none produces albuminuria of marked degree without nitrogen retention.[10]

We have been impressed by the severity of the reaction of the pregnant animal to renal ischemia as compared to that of the nonpregnant one. A review of the literature fails to reveal any evidence to show that other types of renal injury in pregnancy produce a significant difference in reaction. These experiments were designed in an effort to demonstrate the reaction of pregnant animals to various nephrotoxic substances as compared with the nonpregnant animal.

MATERIALS AND METHODS

Thirty-nine female rabbits of from 2.5 to 3.5 kilograms body weight were used as the experimental animals. Twenty-three of these animals were known to be of from eighteen to twenty-two days in the period of gestation and the remaining 16 had been segregated for approximately three weeks to rule out pregnancy and pseudopregnancy. Food consisted of a stock rabbit food and water ad libitum. All ani-

mals were considered to be in good physical condition and were found to be free of spontaneous disease at autopsy.

In the three weeks' control period which preceded the production of renal injury in each of these animals, blood pressure determinations were made by an indirect method[8] twice weekly, urine specimens were collected in metabolism cages and examined for albumin and sediment weekly, and two blood samples were taken for determination of nonprotein nitrogen. Following the procedure carried out to produce renal injury, the blood pressure was determined daily, the urine was examined and the nonprotein nitrogen determination made every other day, until the animal had died or was sacrificed.

All animals not dying within the period of one week were sacrificed by means of 10 per cent formalin intravenously. Routine autopsies were immediately performed; blocks were fixed in Helly's modification of Zenker's solution, embedded in paraffin and stained with hematoxylin and eosin.

In choosing the nephrotic substances an effort was made to use those substances which act more or less specifically on a separate part of the renal apparatus; uranium nitrate,[11] sodium oxalate,[4] and staphylococcus toxin[12] were used. In another group of animals, bilateral ureteral ligation was performed to determine whether this type of renal injury would produce alteration in reaction in the pregnant animal. Many investigators have presented evidence to suggest that ureteral obstruction, pyelitis, and pyelonephritis during pregnancy are predisposing factors to the toxemias of pregnancy.[13] Hypertension has been shown to be present in clinical[14] and experimental[15] ureteral obstruction, and its origin is possibly the same as that seen with renal artery constriction.

In each of the toxins used, an effort was made to employ from one-fourth to one average lethal dose to similar groups of pregnant and nonpregnant animals.

Uranium nitrate was given intravenously in doses of 0.25 mg. and 0.5 mg. per kilogram body weight. Sodium oxalate was given in 3 doses in twelve hours of a 2 per cent solution of normal saline in total doses of 30, 60, and 80 mg. per kilogram body weight, to both pregnant and nonpregnant animals.

Staphylococcus toxin* was given intravenously in 0.025, 0.05 and 0.1 c.c. to both pregnant and nonpregnant animals in two doses in four hours.

Ureteral ligation was performed in the animals of the last group. Under aseptic technique the ureters were doubly ligated and severed, at the junction of the ureter with the renal pedicle.

RESULTS

Uranium Nitrate.—Table I shows the effect of this toxin on four pregnant and four nonpregnant adult rabbits.

The smallest dosages employed (one-fourth of the average lethal dose)[11] caused no change in general condition, nonprotein nitrogen values of the blood, nor significant albuminuria in the pregnant animals. In the nonpregnant animals, however, more apparent injury was sustained; moderate to marked albuminuria, moderate elevations in blood nonprotein nitrogen, and a slight depreciation in general condition were noted. In neither group was there noted to be a significant change in blood pressure, evidence of pathologic liver injury or more than minimal renal injury.

No abortions of fetuses were noted in this group.

The use of the larger dosages (one-half of the average lethal dose) caused a noticeable depression of general condition in both groups of animals and marked albuminuria was uniformly present. The blood nonprotein nitrogen became elevated in all instances and severe renal injury was noted pathologically.

No significant alteration in blood pressure occurred, and the liver showed no gross or microscopic lesions. The difference between the severity of reaction of the two groups is also less marked than in the previous group, and it is noticeable that all pregnant animals delivered or resorbed by the fourth day.

*The staphylococcus toxin used in this study was provided by Dr. A. L. Joyner and the Lederle Laboratories.

TABLE I. THE EFFECT OF URANIUM NITRATE ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	DOSAGE	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
80	0.25 mg.	0	0	90	90	Good	43.1	Neg.	Neg.	Pregnant at time of sacrifice
77	0.25 mg.	1+	4	100	80	Good	51.1	Neg.	Neg.	Pregnant at time of sacrifice
45	0.5 mg.	4+	6	95	112	Fair	62.2	Minimal injury	Neg.	Resorbed on fourth day
56	0.5 mg.	3+	4	85	118	Fair	175.0	Moderate injury	Neg.	Delivered prematurely on fourth day
49	0.25 mg.	3+	5	95	95	Fair	94.6	Moderate injury	Neg.	Not pregnant
53	0.25 mg.	3+	20	65	65	Fair	91.0	------	----	Not pregnant
52	0.5 mg.	4+	6	100	115	Died	252.0	Severe injury	Neg.	Not pregnant
55	0.5 mg.	3+	6	85	110	Good	128.0	Severe injury	Neg.	Not pregnant

*The symbols under "albuminuria" represent:

Amount: tr., No precipitate after heating, slight clouding after acid.
1+, Granular precipitate after heating.
2+, Heavy granular precipitate after heating.
3+, Heavy flocculate precipitate after heating and acid.
4+, Boils solid on heating.

Days: The number of days the albuminuria was present.

†Under "blood pressure" the figures represent the average of blood pressures taken before and after production of renal injury.

TABLE II. THE EFFECT OF SODIUM OXALATE ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	DOSAGE	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
75	30 mg.	0	0	100	95*	Good	48.2	Minimal injury	Neg.	Resorbed on third day
76	30 mg.	0	0	90	80	Good	52.5	Minimal injury	Neg.	Delivered on fourth day
61	60 mg.	tr.	6	75	110	Good	101.5	------	----	Delivered on fourth day
65	60 mg.	3+	5	70	90	Good	80.2	Moderate injury	Neg.	Resorbed on fifth day
64	80 mg.	3+	4	90	80	Fair	243.0	Severe injury	Neg.	Resorbed on fifth day
58	80 mg.	3+	4	95	120	Good	144.0	Severe injury	Neg.	Delivered on fourth day
68	30 mg.	0	0	100	105	Good	46.4	Neg.	Neg.	Nonpregnant
62	60 mg.	tr.	6	90	100	Good	46.0	------	----	Nonpregnant
63	80 mg.	tr.	4	75	110	Good	42.0	------	----	Nonpregnant
54	80 mg.	3+	5	100	120	Fair	200.0	Moderate injury	Neg.	Nonpregnant

* † See footnotes, Table I.

TABLE III. THE EFFECT OF STAPHYLOCOCCUS TOXIN ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	DOSAGE C.C.	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
35	0.025	0	0	90	90	Good	42.0	Neg.	Neg.	Pregnant at time of sacrifice
57	0.050	4+	1	100	90	Died	100.0	Severe injury	Necrosis	
85	0.050	0	0	85	85	Fair	69.0	Minimal injury	Neg.	Delivered at five days
59	0.050	0	0	115	125	Good	54.0	Neg.	Neg.	Pregnant at time of sacrifice
86	0.050	0	0	105	110	Good	44.8	Minimal injury	Neg.	Pregnant at time of sacrifice
36	0.10	0	0	---	---	Died	----	Neg.	Neg.	Died one hour after injection
37	0.10	0	0	---	---	Died	----	Neg.	Neg.	Died one hour after injection
38	0.025	0	0	90	90	Good	40.0	Neg.	Neg.	Nonpregnant
88	0.050	0	0	95	100	Good	36.7	Neg.	Neg.	Nonpregnant
60	0.050	2+	4	90	90	Poor	160.0	Neg.	Neg.	Nonpregnant
87	0.050	0	0	112	110	Good	53.3	Neg.	Neg.	Nonpregnant
75	0.050	0	0	100	95	Good	48.0	Minimal injury	Neg.	Nonpregnant
39	0.10	0	0	---	---	Died	----	Neg.	Neg.	Died one hour after injection
40	0.10	0	0	---	---	Died	----	Neg.	Neg.	Died one hour after injection

* † See footnotes, Table I.

TABLE IV. THE EFFECT OF BILATERAL URETERAL LIGATION ON THE GENERAL CONDITION, BLOOD PRESSURE, AND RENAL STATUS OF THE PREGNANT AS COMPARED WITH THE NONPREGNANT RABBIT

RABBIT NO.	PROCEDURE	ALBUMINURIA*		BLOOD PRESSURE†		GENERAL CONDITION	HIGHEST N.P.N.	AUTOPSY		OUTCOME OF PREGNANCY
		AMOUNT	DAYS	BEFORE	AFTER			KIDNEYS	LIVER	
73	Ureters ligated	----	----	90	too low	Died	166	------	----	Delivered at four days
74	Ureters ligated	----	----	90	too low	Died	90	Severe injury	Neg.	Pregnant at time of sacrifice
66	Ureters ligated	----	----	100	115	Died	168	Severe injury	Neg.	Delivered at four days
67	Ureters ligated	----	----	90	100	Died	150	Severe injury	Neg.	Nonpregnant
70	Ureters ligated	----	----	100	135	Died	200	------	----	Nonpregnant
69	Ureters ligated	----	----	100	110	Died	224	------	----	Nonpregnant

* † See footnotes, Table I.

One animal in the nonpregnant group died of uremia; no deaths were encountered in the pregnant group.

Sodium Oxalate.—Table II shows the effect of intravenous injections of varying dosages of sodium oxalate on 6 pregnant and 4 nonpregnant adult rabbits.

All animals, both pregnant and nonpregnant, following injection with the smallest dosages of sodium oxalate showed no significant change in general condition, urinary findings, or blood pressure, and no nitrogen retention was noted. Pathologic study revealed no renal or hepatic damage. Both pregnant animals resorbed the fetuses or delivered by four days, however.

Moderate dosages of sodium oxalate produced mild elevation of blood pressure and slight albuminuria in both groups of animals. The general condition remained good and no abnormal hepatic pathology was noticeable, although renal injury was present to a minimal degree. An elevation of blood nonprotein nitrogen was noted only in the pregnant group and resorption or delivery of fetuses was accomplished in both instances by the fourth day.

Large doses of sodium oxalate produced a mild elevation of the blood pressure, moderate albuminuria, and marked elevation of the blood nonprotein nitrogen in both pregnant animals and in one of the two nonpregnant ones. The remaining nonpregnant animal showed evidence of renal injury, but not of such severe nature. All pregnant animals had resorption or delivery of fetuses by the fifth day. Pathologic sections showed marked renal injury but no hepatic damage.

Staphylococcus Toxin.—Table III shows the effect of varying dosages of this toxin on 7 pregnant and 7 nonpregnant adult female rabbits.

The animals receiving very small doses of this substance showed no evidence of clinical or pathologic injury.

In general all animals, both pregnant and nonpregnant, receiving moderate dosages, remained normal. In one animal in each group, however, moderate to severe albuminuria, nitrogen retention, and severe damage to the renal cortex pathologically were noted. Two animals in the pregnant group were noted to have rare areas of midzonal necrosis of the liver lobule; one of these had severe renal injury. Significant alterations in blood pressure were not noted in any of these animals.

All animals receiving the larger dosages of toxin died immediately after injection and no pathologic lesions were noted.

Large doses produced severe albuminuria, a moderate elevation in blood pressure and nitrogen retention in both the pregnant and nonpregnant groups of animals. Pathologically the renal damage was noted to be severe; in one animal rare but definite midzonal areas of necrosis in the liver were noted. The resorption of fetuses occurred in all pregnant animals.

It seemed quite noticeable in all animals except one that the pregnant animal received more injury from this drug than that noted in the nonpregnant one, as evidenced by the degree of albuminuria, level of the nonprotein nitrogen in the blood, and pathologic evidence of renal injury. No significant difference in the blood pressure levels could be determined.

Ureteral Ligation.—Ureteral ligation produced a steadily rising nonprotein nitrogen level in the blood and a depression of the general condition in all animals. All nonpregnant animals developed a mild rise of blood pressure but all but one of the pregnant animals had a decided fall in pressure. Delivery was noted in two of the pregnant animals before death.

Pathologic sections showed extreme damage to the kidneys but no evidence of injury to the liver.

The effect of ureteral ligation on 3 pregnant and 3 nonpregnant adult rabbits is given in Table IV.

DISCUSSION

It seems that the response of the pregnant animal toward different types of renal injury differs slightly from that of the nonpregnant animal and also with the type of injury produced.

Uranium nitrate seems to exert a somewhat less harmful effect during pregnancy, while sodium oxalate seems more injurious. The difference in individual susceptibility of animals to staphylococcus toxin and the fact that all animals with ureteral ligation die in uremia with marked renal destruction makes the effect of these two types of renal injury harder to evaluate; however, the pregnant animal does not seem to differ significantly in response from the nonpregnant animal.

Any striking variation in reaction which might be expected in the pregnant animal is undoubtedly modified by the fact that abortion or resorption of fetuses generally occurs soon after the production of kidney injury; in this way the effects of pregnancy are exerted only in the earliest stages of the experiment.

Significant variations in blood pressure are not noted following renal injury by uranium or staphylococcus toxin. Ligation of the ureters seems to produce a modest rise in pressure in the nonpregnant animal, but none in the pregnant one, while sodium oxalate produces a mild elevation of pressure in both the pregnant and nonpregnant animals.

No significant constant necroses in the liver or other organs were produced by any of these substances except the staphylococcus toxin, and these are found in the nonpregnant as well as in the pregnant animal. The small number of animals in this series makes evaluation of such injury in the presence of extreme differences in susceptibility of individual animals extremely hazardous, but this type of injury seems quite promising for further investigation.

None of these methods will reproduce with regularity either the clinical picture, the pathologic changes, or the increased susceptibility in the pregnant state such as that seen following constriction of the renal arteries of the rabbit. It seems that the renal ischemia, both in the pregnant and nonpregnant animal is not the result of nonspecific injury as such but is a definite entity caused by a specific type of alteration of renal physiology.

CONCLUSIONS

Pregnancy does not exert a deleterious effect on all types of renal injury.

The pregnant animal seems to be minimally less susceptible than the nonpregnant one to uranium nitrate, slightly more susceptible to sodium oxalate, and demonstrates no significant difference to staphylococcus toxin or ureteral ligation.

The syndrome produced by renal artery constriction in the pregnant and nonpregnant animal is not due to renal damage as such, but is apparently caused by a relatively specific type of altered renal physiology.

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THE METABOLISM OF PROGESTERONE IN THE HYSTERECTOMIZED WOMAN

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THE role of the uterine endometrium as a metabolic or endocrine organ has long been of interest to both the physiologist and clinician. Numerous observations have been made on experimental animals which tend to support the theory of such a uterine function. Most notable among these is the classic work of Loeb in which he demonstrated that a persistent corpus luteum followed hysterectomy in the guinea pig.

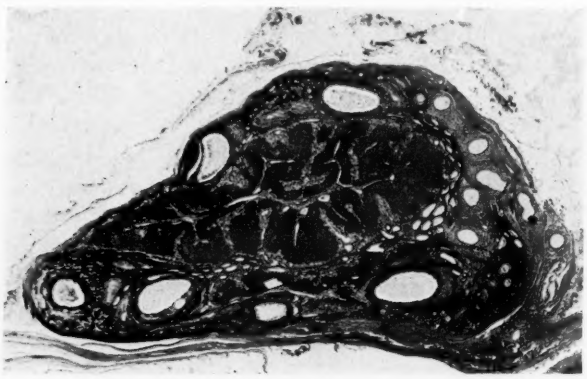

Fig. 1.—Low power photomicrograph of the ovary of a monkey *Macacus* (Pithecus) *rhesys*, removed 15 months after a panhysterectomy. Monkey 21, through the courtesy of Dr. Carl G. Hartman of the Carnegie Institution.

This work has recently been repeated on the rabbit by Asdell and Hammond. No one, however, has demonstrated such a mechanism in the primates, and Hartman has observed regular ovulations following hysterectomy in the *Macacus rhesus*. Through the courtesy of Dr. Carl Hartman of the Carnegie Institution, the ovarian sections of one of his hysterectomized monkeys has been made available to us for publication (Fig. 1). The case history of this animal, No. 21, has been presented in the Contributions to Embryology for 1928, and is interesting in that she continued to have vaginal estrous cycles and changes in the sex swelling as long as fifteen months after a panhysterectomy. A histologic examination of the ovaries at autopsy showed numerous primordial follicles, Graafian follicles in all stages of development, and

several corpora lutea aberrentia. Dr. Corner has been kind enough to examine the slides and feels that, although the corpora probably date from several months back, it is unlikely that they are over a year old.

A much earlier piece of work is that published by Mandl and Buerger in 1904. These observers examined the ovaries of apes from six months to three years after hysterectomy and found follicles in all stages of development, including well-formed corpora lutea; however, fewer primordial follicles were seen and blood was noted in many of the larger follicles. The authors, therefore, concluded that there may be some questionable atrophy of the ovaries following hysterectomy in the ape. Glaevecke, Vineberg and Grammatikati each performed similar examinations on human ovaries, six months to three years after removal of the uterus, and were unable to demonstrate any histologic changes from the normal. Such experiments are, of course, open to criticism, in that they attempt to judge function on the basis of morphology.

Aside from these early histologic efforts, the problem in the human being has been approached by three different methods. The first of these was a clinical study of the onset of menopausal symptoms following hysterectomy. The results of such studies were inconstant and interpretation was difficult. Although some authors believe that hysterectomy induces a premature menopause, the possibility of damage to the ovary, through interference with its blood supply at operation, is a factor which must always be considered in studies of this type and which cannot be accurately evaluated.

The older literature on this subject is well summarized by Graves in a paper in 1917. All observers up to that time, with the exception of Dickinson, were of the opinion that hysterectomy alone was as frequently followed by menopausal symptoms as was hysterectomy and bilateral salpingo-oophorectomy. Graves' figures agree with this majority opinion, for, in his series, 80 per cent of 233 cases of hysterectomy and bilateral salpingo-oophorectomy and 81 per cent of 26 cases of simple hysterectomy were associated with menopausal symptoms. TeLinde and Darner, in a more evenly divided series of 98 cases, found that 74 per cent of 52 women, who had had the radical operation, developed menopausal symptoms, while they appeared in only 47 per cent of 46 cases after a simple hysterectomy. It was also noted that the severity of symptoms was much greater following hysterectomy and bilateral salpingo-oophorectomy than after the more conservative operation. Cystic ovaries were never seen postoperatively in those cases where it was possible to retain the Fallopian tubes. That the problem is still a subject of debate can be seen from a discussion by A. H. Curtis in the *American Gynecological Society Transactions* of 1939 in which he states "If the cervix is removed the ovaries degenerate in two to three years; naturally, if the cervix is left the ovaries do not degenerate."

The second approach to the problem came with the advent of blood and urine estrogen determinations. Tamis, in 1934, and Marx, Catchpole and McKennon, in 1936, attempted to evaluate ovarian function after hysterectomy by correlating menopausal symptoms with estrogenic excretion. Here again the results were equivocal. Although methods for estrogen determination have greatly improved since the publication of these reports, the chemical accuracy of such studies is still highly questionable. The most recent work along these lines is probably that of

Smith and Smith who, in 1939, concluded that progesterone, acting through the uterus (presumably the endometrium) brings about the conversion of estrone to estriol. The evidence of this, however, does not seem to be based on any studies in the hysterectomized human being but on work performed on the rabbit by Pincus and Zahl. In this work five hysterectomized rabbits were injected with estradiol and estrone in various experiments and the partition of the estrogenic substances was estimated in the urine. The David color reaction was used as a measure of estriol and the phenol-sulfonic acid and sulfanilic acid tests of the estrone and estradiol excretion. Although this work is interesting it would seem that isolation of the true chemical substances would be a much safer basis for so broad a theory.

With the publication of the Browne and Venning method for the determination in the urine of sodium pregnanediol glucuronidate, the excretion product of the corpus luteum, a third and more satisfactory technique for the study of the hormonal metabolism of the uterus, has become available. This approach offers two great advantages over the former methods. First, the method is chemically accurate, and second, it demonstrates the presence of a functioning corpus luteum, which is commonly assumed to be an index of ovulation and is therefore better proof of the normal cyclical function of the ovary.

The problem has been approached from this angle by several observers. Browne and Venning, in the discussion of a paper which appeared in 1937, first suggested that pregnanediol failed to appear in the urine of hysterectomized women who had been injected with progesterone, indicating a failure of conversion of progesterone into pregnanediol in the absence of the uterus. A further note was published in 1938 in which it was stated that two hysterectomized patients, each of whom had been injected with 24 mg. of progesterone, failed to excrete pregnanediol. In 1940, however, they report the recovery from the urine of a hysterectomized patient of 8.6 mg. of pregnanediol after the injection of 90 mg. of progesterone over a three-day period. Hamblen in 1937, on the basis of a study of four cases, concluded that the endometrium was necessary for the conversion of progesterone into pregnanediol. An analysis of his cases shows that only one was hysterectomized and this patient excreted 4 mg. of sodium pregnanediol glucuronidate on the fourth day postoperatively. The other three cases studied were patients upon whom a dilatation and curettage had been performed. Of these, one was operated upon on the twenty-third day of the cycle. She excreted 2.6 mg. of the pregnanediol complex the first day postoperatively and none the second day, that is the twenty-fifth day of the cycle. From the figures of Browne and Venning very little, if any, pregnanediol is excreted so late in the luteal phase of the cycle and small amounts in a twenty-four-hour specimen can easily be lost through technical errors. The second patient, who was curetted on the twenty-third day of the cycle, failed to excrete pregnanediol following the procedure. However, as this patient was not excreting pregnanediol before curettement, the case is of little value. The third patient was operated upon on the twenty-fifth day of the cycle and was excreting only 1.4 mg. of the pregnanediol preoperatively, which probably means that this patient was at the end of her luteal phase. It is, therefore, not surprising that on the twenty-sixth and twenty-seventh days of her cycle she excreted no pregnanediol. Criticism of this work seems justifiable, in that too few cases have been used to draw any conclusions from such purely negative evidence. It is also erroneous to assume that a dilatation and curettage removes all or nearly all of the endometrial tissue.

Stover and Pratt, in 1939, reported the case of a patient upon whom a hysterectomy was performed on the one hundred and forty-second day of pregnancy. This

patient continued to excrete pregnanediol during the first five days postoperatively. The authors raise the question of the possibility of stored pregnanediol.

The present study was undertaken in an attempt to evaluate such conflicting results in the literature. An effort was first made to determine the percentage of progesterone which was recoverable as pregnanediol in a normal woman in the follicular phase of the cycle. Pregnanediol determinations were then made on the urine of hysterectomized women who had been injected with progesterone and also on several patients who were estimated to be in the luteal phase of the cycle by testing the cervical mucus. In this way it has been possible to gain some idea of both exogenous and endogenous progesterone metabolism. The pregnanediol determinations were performed by a modification of the Browne and Venning technique previously described.

CASES

GROUP 1.—A normal woman in the follicular phase of her cycle was given an injection of 120 mg. of crystalline synthetic progesterone* in 10 mg. doses, four times a day, over a period of three days. The urine was collected over the entire injection period and the sodium pregnanediol glucuronidate content was determined. With this figure as an index of possible recovery, 3 hysterectomized patients were injected in a similar manner and pregnanediol determinations were performed on the urine. Pregnanediol was recovered in amounts comparable to those found in the patient with endometrium intact (Table I). It can be seen from the table that not more than 15 per cent of the injected progesterone has been recovered as pregnanediol. These figures should not be used as an absolute index of recovery,

TABLE I

PATIENT	OPERATION	PROGESTERONE INJECTED	PREGNANEDIOL* RECOVERED	TOTAL % RECOVERED
D. A.	None	1st day 40 mg. 2nd day 40 mg.	9.5 mg.	
		3rd day 40 mg.	4.3 mg.	
			13.8 mg.	11.5
J. B.	Panhysterectomy	1st day 40 mg.	2.6 mg.	
		2nd day 40 mg.	7.2 mg.	
		3rd day 40 mg.	4.7 mg.	
			14.5 mg.	12.0
		4th day none 5th day none	4.2 mg.	
			18.7 mg.	15.6
M. S.	Hysterectomy Bilateral sapingo-oophorectomy	1st day 60 mg.	5.3 mg.	
		2nd day 60 mg.	3.5 mg.	
		3rd day 60 mg.	9.6 mg.	
			18.4 mg.	10.2
		4th day none	3.0 mg.	
		5th day none	1.9 mg.	
			23.3 mg.	12.9
M. M.	Hysterectomy	†1st day 60 mg.	4.9 mg.	
		2nd day 60 mg.	9.6 mg.	
		3rd day 60 mg.	5.1 mg.	
			19.6 mg.	10.9

*Values calculated as free pregnanediol according to Venning: J. Biol. Chem. **126**: 595, 1938.

†Twenty-sixth day of calculated cycle.

*Synthetic lutocylin through the courtesy of the Ciba Corporation.

however, as more attention was given to the purity of the pregnanediol recovered than to the completeness of the recovery. The combined pregnanediol precipitates were frequently precipitated 3 times instead of the customary two. The melting points of the combined pregnanediol specimens ranged between 257° and 266° C. uncorrected, and the free between 222° and 234° C. uncorrected.

As the amount of progesterone injected in these cases was more than that used by most other investigators and was also injected over a period of three days, a hysterectomized case was injected with only 60 mg. of progesterone over a period of six hours. It was thought that such a case might be more comparable to those reported in the literature. Twenty-four-hour collections were made during the injection period and over the two succeeding days. Traces of pregnanediol were recovered on all three days, but the amounts were too small to be identified by melting points.

GROUP 2.—The next case studied was a patient who had had a panhysterectomy on the first day of her menstrual cycle. Pregnanediol determinations were performed on the forty-eight-hour specimens of urine on the twelfth and thirteenth and on the fourteenth and fifteenth days of the cycle. No pregnanediol could be demonstrated. On the sixteenth and seventeenth days 6.1 mg. of the pregnanediol complex, having a melting point of 264° to 265° F., was recovered.

GROUP 3.—Three cases, which had had hysterectomies performed six months or more previously, were studied by following the cervical mucous secretion weekly during a period of one month. All three patients exhibited changes in the pH, viscosity, and the spermatozoa penetrability indicative of a normal ovarian cycle. From these studies it was attempted to approximate the luteal phase and a twenty-four-hour collection of urine was obtained during this period. Three and three-tenths milligrams of pregnanediol was recovered in one out of three of these specimens. It is felt that, because of the very rough approximation of the time of the luteal phase in these patients, it is not surprising that two of the twenty-four-hour specimens were negative.

DISCUSSION

The data which have been presented seem to demonstrate that the presence of the uterine endometrium is not necessary for the conversion of progesterone into pregnanediol. It is probable that the normal ovarian cycle, with the formation of the corpus luteum, is uninterrupted following hysterectomy. This fact is supported by the occurrence of normal amounts of pregnanediol in the urine of two women, one of whom was hysterectomized on the first day of the current menstrual cycle and the other more than six months before.

It has never been possible, in this laboratory, to recover more than 15 per cent of injected progesterone as pregnanediol. Recovery is more satisfactory if the patient is injected over a period of days. It is felt that some of the negative results in the literature might be explained on the basis of inadequate amounts of hormone injected.

SUMMARY

Progesterone has been injected into hysterectomized women and recovered, in part, in the urine as pregnanediol. The percentage recovered was the same as that observed for a normal woman in the follicular phase of the cycle who was injected with an equal amount of the hormone. Pregnanediol, in amounts comparable to those found in normal cyclic women, was recovered from the urine of hysterectomized women at a time when they were estimated to be in the luteal phase of the cycle.

It is estimated that the hysterectomized woman is able to metabolize both exogenous and endogenous progesterone.

The authors wish to express their appreciation to Dr. Landrum B. Shettles for his advice and assistance in the cervical mucus studies and to the Ciba Corporation for a very generous supply of lutocylin.

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A CLINICAL STUDY OF PROGESTERONE THERAPY BY PELLET IMPLANTATION

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PROGESTERONE is now used in clinical gynecology for the treatment of habitual abortion, functional bleeding, dysmenorrhea, and premenstrual tension. Intramuscular injections in doses of 1 to 5 mg. have been the usual method of therapy. Recently, an oral progesterone-like substance, pregneninolone, has been tried with some degree of success. In 1938, Deanesly and Parkes[1] reported the results of implantation into rabbits of progesterone tablets, 5.1 mg. in weight. Five days after the implantation, they found full progesterone effect in the uterus of the immature animal, which had previously been sensitized with estrone. They found the total absorption during the period was 1.5 mg. They suggested the clinical trial of implantation in cases of habitual abortion, where a steady, prolonged progesterone effect is desired.

During the past year, we have been gratified by the clinical results obtained with implantation of pellets of estrone in the treatment of the menopause. We found that a prolonged, continuous absorption of a small amount of hormone over a long period of time resulted from this method of therapy. It has been the observation of some clinicians[2] that in cases of habitual abortion, small doses of progesterone injected daily are more effective than large amounts administered once or twice a week. We decided to try the administration by implantation of progesterone tablets weighing 45 to 60 mg. in a group of cases in which

progesterone therapy appeared to be indicated. These cases are divided into several groups; namely, habitual or threatened abortion, dysmenorrhea, and functional bleeding. In the latter two groups, we were able to obtain endometrial biopsies before and after treatment.

Under ½ per cent novocaine anesthesia, an incision less than 1 cm. in length is made in the skin in the region of the left groin. A channel, 2 cm. in length, is made with a small curved hemostatic forceps. The forceps are withdrawn, and the pellet inserted into the bed thus formed. The edges of the incision are strapped together with sterile adhesive. No sutures are used. This procedure takes but a few seconds longer than an intramuscular injection. The incision heals by primary union within twenty-four hours. No immediate adverse symptoms or side reactions have been observed. However, in 35.7 per cent of the cases, the pellet has been expelled spontaneously two or three weeks after implantation. In these cases, reimplantation has been performed successfully.

GROUP I. HABITUAL AND THREATENED ABORTION

Four cases were observed. One, delivered at full term, is briefly described as follows:

M. S., aged 28 years: Habitual abortion following primary sterility. Previous treatment for sterility: thyroid, and substitution estrone and progesterone therapy by intramuscular injection. No results. X-ray stimulation to pituitary and ovaries. Conception one month later. Spontaneous miscarriage at five months. Patient conceived four months later and miscarried again at six weeks. Two months later conception took place for the third time. At four and one-half months patient experienced cramps similar to those at time of first miscarriage. Implantation with 62.8 mg. of progesterone was done May 16, 1940. This pellet was expelled spontaneously on June 3, 1940. Reimplantation of 45 mg. was done the same day. Pains completely disappeared a few days after first implantation and the pregnancy continued uneventfully to term.

The other cases are still under observation. It should be noted that no miscarriage occurred in any of the 4 patients treated.

M. S., aged 34 years: Habitual abortion. History of spontaneous miscarriage at two and one-half months in 1937, and at three and one-half months in 1939. Last menstrual period March 5, 1940. Implantation of 52 mg. of progesterone was done June 3, when the patient was eight weeks gravid. The course of this pregnancy has been uneventful to date (eight months). (Courtesy of Dr. Lyman Burnham.)

D. F., aged 28 years: Threatened abortion. History of spontaneous miscarriage at two months in 1939. Last menstrual period July 30, 1940. Patient reported spotting on several occasions during this pregnancy. Implantation of 49 mg. of progesterone on Sept. 9, 1940, when patient was six weeks gravid. There has been no spotting since September 11; pregnancy at present is of three months' duration. (Courtesy of Dr. Lyman Burnham.)

J. T., aged 28 years: Threatened abortion. History of spontaneous miscarriage at three months in 1936. Last menstrual period May 8, 1940. Cramps and vaginal bleeding Aug. 12, 1940. Implantation of 49 mg. of progesterone on Sept. 20, 1940. Pains subsided after implantation. Examination Nov. 14, 1940, disclosed normal pregnancy of six months.

GROUP II. DYSMENORRHEA

T. S., aged 26 years: Primary dysmenorrhea. Examination: uterus normal in size and position. No adnexal masses. Basal metabolic rate −14 per cent. Previous therapy: Pelvic sympathectomy three years ago. Recurrence of symptoms past two years. Biopsy (Fig. 1) taken on March 26, 1940, the eighteenth day of the cycle, revealed moderate proliferative activity, no evidence of secretory phase.

Biopsy (Fig. 2) taken April 2, 1940, the twenty-fifth day of the cycle, showed slight evidence of secretion, dense stroma. Abortive secretory phase. Implantation of 56 mg. of progesterone was done on May 18, 1940. Menstrual period started twelve days later and lasted for seven days. There was increased flow and severe pain the first two days. On the fourth day of the period the progesterone pellet was spontaneously extruded. Second implantation, this time 49.5 mg. of progesterone was given on June 8, 1940. (Five days after extrusion of pellet.)

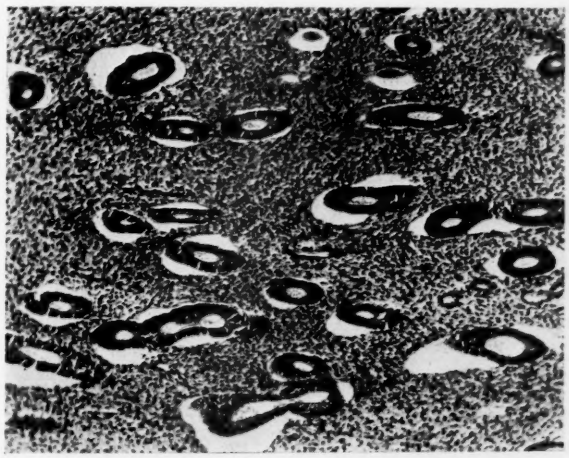

Fig. 1.—Primary dysmenorrhea (T. S.) (before therapy). Endometrial biopsy taken on eighteenth day of cycle. Moderate proliferation. No evidence of secretory phase.

Fig. 2.—Primary dysmenorrhea (T. S.) (before therapy). Endometrial biopsy taken on twenty-fifth day of cycle. Slight evidence of secretion, dense stroma. Very little evidence of progesterone activity.

Menstrual history after reimplantation as follows:

July 8, 1940, duration eight days. No pain for the first time in two years.
Aug. 3, 1940, duration six days. Moderate flow, slight pain first day.
Sept. 8, 1940, duration seven days. Moderate discomfort second and third day.
Oct. 3, 1940, duration seven days. No pain.
Nov. 7, 1940, duration seven days. No pain.

Biopsy taken Sept. 30, 1940 (Fig. 3), the twenty-third day of the cycle, revealed a well-developed secretory phase with marked decidual reaction.

M. R., aged 20 years: Severe dysmenorrhea past five years. Examination essentially negative. Uterus normal by rectal examination. Menstrual history: onset eleven years, interval twenty-four days, duration two to four days. Implantation of 55 mg. of progesterone was done on Aug. 10, 1940. Menstrual history after implantation as follows:

Aug. 11, 1940, duration four days. Regular flow, severe pain.

Sept. 2, 1940, duration five days. Profuse flow. Slight cramps only for a few hours. No time lost from work, whereas previously patient lost one to two days.

Sept. 26, 1940, duration five days. Decreased flow, no pain.

Oct. 21, 1940, duration five days. Normal flow. Backache first day, but no pain.

R. R., aged 28 years: Primary dysmenorrhea. Examination: normal-sized uterus, freely movable. Right ovary enlarged to size of plum and tender. Menses: Onset at 14 years, irregular and prolonged intervals five to seven weeks, duration four to five days. First two days, moderate flow, then scant. Previous therapy: thyroid, gr. ½, t. i. d. Biopsy taken on Aug. 30, 1940, the fifteenth day of the cycle, revealed a hypoplasia and slight proliferative activity. Biopsy taken on Sept. 5, 1940, the twentieth day of the cycle, showed an abortive secretory phase. Implantation was done Sept. 5, 1940, with 55 mg. of progesterone. Menstrual period

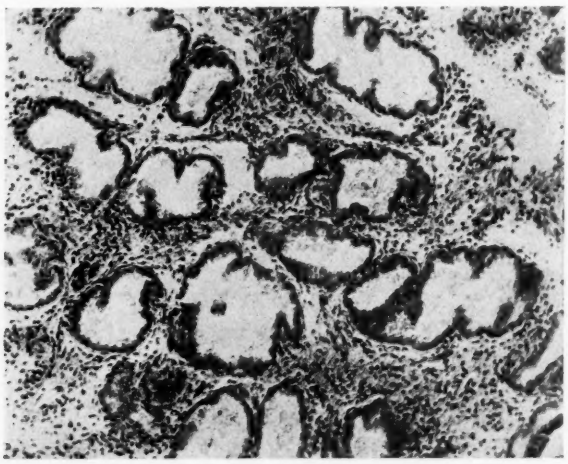

Fig. 3.—Primary dysmenorrhea (T. S.) (after therapy). Endometrial biopsy taken on twenty-third day of cycle. Well-developed secretory phase.

on Sept. 15, 1940, for five days. Patient stated: "This period began with less pain than I have ever known." Examination Oct. 7, 1940: right ovary normal in size. The following month patient experienced severe pain again. An additional implantation was done on Oct. 18, 1940, with 55.5 mg. of progesterone. Menstrual period began on October 22, duration four days. No pain with this period.

F. M., aged 30 years: Severe dysmenorrhea and premenstrual nausea. Examination: uterus normal. Basal metabolic rate −4 per cent. Menses: onset at 15 years, intervals four to seven weeks, duration eight days. Now flows only three days. Implantation of 47 mg. of progesterone on June 22, 1940. Menstrual history after implantation:

June 26, 1940, duration four days. Felt well, no pain. Best period since onset.

July 19, 1940, duration one day. No pain.

Aug. 17, 1940, duration two days. No pain or nausea.

Sept. 29, 1940, duration two days. Slight pain day before onset. Pellet practically absorbed.

O. M., aged 21 years: Severe dysmenorrhea. Rectal examination disclosed a small uterus. Menses: onset at age of 14 years, interval twenty-eight to thirty-four days, duration five to seven days. Previous therapy: preliminary course of estrone, 10,000 I. U. by injection three times weekly for two weeks. Implantation

of 48.5 mg. of progesterone on June 10, 1940. Patient experienced premenstrual cramps on June 14. Menstrual history following implantation:

June 16, 1940, duration five days. Decreased flow, but less pain than any time since onset.

July 4, 1940, duration five days. Eighteen-day interval. Cramps first day.

Aug. 7, 1940, duration four days. Severe pain first day. Pellet extruded spontaneously.

Reimplantation with 49.5 mg. of progesterone on Aug. 19, 1940. Menstrual periods as follows:

Sept. 7, 1940, duration five days. Moderate cramps first day.

Oct. 14, 1940, duration six days. No pain, normal flow.

E. K., aged 18 years: Primary dysmenorrhea. Examination: uterus small. Basal metabolic rate −6½ per cent. Menses: onset at 14 years of age, interval twenty-eight days, duration four days. Previous therapy: estrone 10,000 I. U. three times weekly by injection. Implantation of 53 mg. of progesterone on Sept. 7, 1940. Menstrual history after implantation:

Sept. 13, 1940, duration four days. Severe pain at onset, but not as severe as before implantation.

Oct. 12, 1940, duration four days. Best period since onset. No pain, nausea, or vomiting. Patient still under observation.

GROUP III. FUNCTIONAL BLEEDING

E. M., aged 19 years: Menorrhagia. Menses: onset at 11½ years of age, intervals three to four months, duration seven days, profuse flow. Past four months, periods prolonged two weeks' duration. Examination: eunuchoid type, span 67 inches, upper 30 inches, lower 37 inches. Basal metabolic rate −15 per cent. Hair and breasts normal. Biopsy (Fig. 4) taken on May 18, 1940, 27 days after onset of period shows a proliferative endometrium and physiologic hypertrophy. Implantation of 45.5 mg. of progesterone on June 1, 1940. Menstrual history following implant:

May 29, 1940 to June 5, 1940, June 24, 1940 to July 3, 1940, July 27, 1940 to Aug. 4, 1940, Aug. 24, 1940 to Aug. 31, 1940.

Normal flow each period.

Biopsy (Fig. 5) taken on the twenty-fifth day of the cycle, Aug. 21, 1940, reveals a functioning secretory phase.

A. G., aged 27 years: Menorrhagia. Menses: onset at 13 years of age, intervals four to seven weeks, duration seven days, profuse flow. Examination: bilateral cystic ovaries. Operation in November, 1939, partial resection bilateral cystic ovaries. Four months later, recurrence of symptoms as before. Biopsy taken in October, 1938, revealed an anovulatory endometrium. Biopsy taken in April, 1940, showed an abortive secretory phase with cystic glands. Implantation of 58.4 mg. of progesterone was done on May 16, 1940. Menstrual periods after implantation follow:

June 14, 1940, duration four days. Half in amount of period previous. Patient felt well.

July 16, 1940, pellet was spontaneously extruded. Since then periods have become as profuse as prior to therapy.

E. N., aged 28 years: Menorrhagia, metrorrhagia six months. Menses: onset at 13 years of age, interval twenty-eight days, duration four to five days. Examination revealed right ovary twice normal size. Basal metabolic rate +15 per cent. Biopsy taken on April 6, 1940, revealed a proliferative endometrium, mild local atrophy. Menstrual period April 15, 1940. Biopsy taken May 11, 1940, on the twenty-sixth day of the cycle, revealed an early proliferative phase; anovulatory endometrium. Implantation of 46 mg. of progesterone was done on June 1, 1940. Menstrual history following implantation:

June 13, 1940, less profuse, and no pain. Staining two days before onset, duration four days, no clots.

July 7, 1940, duration six days, regular in amount.

August 4, 1940, duration eight days, more profuse.
Biopsy taken July 3, 1940, on the twenty-fifth day of the cycle revealed a secretory phase.

A. W., aged 22 years: Menorrhagia, and metrorrhagia since delivery ten months ago. Menses: onset at 14 years of age, intervals two to three months, duration seven days. Previous therapy: Gonadotropic hormone 100 R. U. 3 times weekly. Bleeding September 2 to 11, using 12 to 15 pads daily. Biopsy taken on Sept. 7, 1940, showed an atrophy of the endometrium with irregularity of build. Implantation of 61.5 mg. of progesterone was done on Sept 7, 1940. Menstrual period

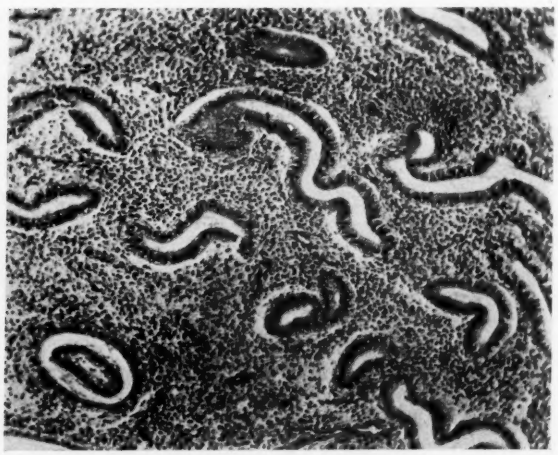

Fig. 4.—Functional bleeding (E. M.) (before therapy). Endometrial biopsy taken on twenty-seventh day of cycle. Marked proliferation. No evidence of secretion.

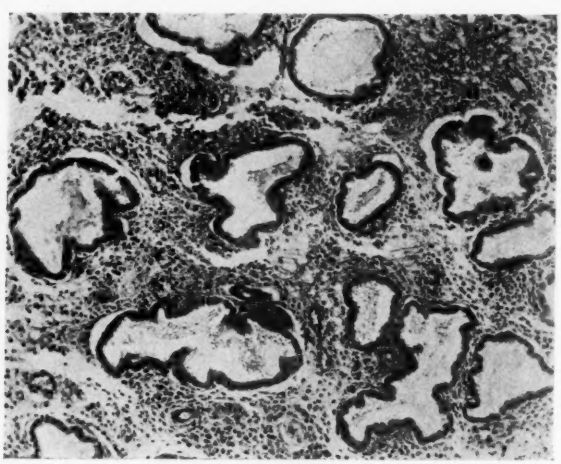

Fig. 5.—Functional bleeding (E. M.) (after therapy). Endometrial biopsy taken on twenty-fifth day of cycle. Functioning secretory endometrium.

September 22 to 27. On October 3, pellet extruded. Reimplantation with 56 mg. of progesterone on Oct. 5, 1940. Oct. 9, 1940, bleeding continued intermittently. Patient was referred for radiation therapy to pituitary gland.

DISCUSSION

Group I. Habitual and Threatened Abortion.—Of the 4 patients treated, one was delivered at full term. The second is now eight months

pregnant, and may thus be considered a successful result. The third, threatened abortion, is now three months pregnant, and is still under observation. The fourth is now six months gravid and is apparently a successful result. The results in this preliminary group of cases seemed to warrant prophylactic implantation with progesterone. This procedure was carried out in several cases of primary sterility where conception has taken place following x-ray stimulation to the pituitary and ovaries. It may be advisable to administer progesterone to any true sterility case as soon as conception has been definitely established in order to increase the capacity of the endometrium for nidation.

Group II. Dysmenorrhea.—Of the 6 cases reported, satisfactory results were obtained in 4 patients. These cases were observed for a period of three to six months, during which time the menstrual periods were almost entirely free of pain. In 3 cases, the pellets were extruded spontaneously after two to three weeks, but were retained upon reimplantation.

Group III. Functional Bleeding.—Clinical cures were obtained in 50 per cent of this small group of cases. In the successful cases, the endometrium showed a change from a persistent proliferative or abortive secretory phase to a well-developed secretory phase. These definite histological changes of the endometrium seem to indicate that the action of progesterone by implantation is effective. In one unsuccessful case (A. W.), a preliminary study of the endometrium showed no evidence of either estrone or progesterone activity. This case might have responded to progesterone, had we primed the endometrium beforehand with a sufficient amount of estrone, as it is well known that progesterone acts only upon an endometrium which has been stimulated previously by estrone. This fact is substantiated by evidence of estrone effect in the endometrium of our 2 successful cases, obtained before therapy was instituted. This emphasizes again the need for a complete endometrial study before institution of therapy.[3]

CONCLUSIONS

1. Satisfactory results were obtained in a small group of cases of habitual abortion, threatened abortion, and in cases of primary dysmenorrhea.

2. Satisfactory results were also obtained in 50 per cent of cases of functional bleeding.

3. As a result of these preliminary investigations, implantation therapy seems worthy of a further clinical trial.

I desire to thank Dr. Leon Motyloff, Pathologist to the Woman's Hospital, for the preparation and study of the endometrial specimens.

NOTE.—The progesterone pellets used in this study were pure synthetic alpha progesterone m.p. 128-130. The finely powdered material was compressed in a steel die punch tablet machine without addition of any inert diluent. The material was furnished through the courtesy of Dr. C. F. Longfellow of G. W. Carnrick Co., Newark, N. J.

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THE INCIDENCE OF ENDOMETRIAL HYPERPLASIA WITH UTERINE FIBROIDS AND EXTERNAL AND INTERNAL ENDOMETRIOSIS (ADENOMYOSIS)*

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TO INVESTIGATE the relationship of endometrial hyperplasia to uterine fibroids and endometriosis, we have reviewed the microscopic pattern of the endometrium in 727 uteri, containing one or more fibroid tumors, 108 cases of extrauterine endometriosis, and 82 cases of intrauterine endometriosis (adenomyosis).

The endometrium was classified as early or late proliferative, secretory, menstruating, pregnant, hyperplasia, and senile. Our diagnosis of endometrial hyperplasia is based on variation in size and shape of the endometrial glands, with large glands being characteristic. The glandular epithelium shows no evidence of secretion, the nuclei are large hyperchromatic, and mitotic figures are numerous. The stroma is compact and avascular. The individual stromal cells are small with hyperchromatic nuclei and scant cytoplasm. Mitotic figures are present but not as numerous as in the glandular epithelium. A normal endometrium of the late proliferative pattern presents many of these characteristics, and it is often difficult to decide in such endometria whether or not a diagnosis of hyperplasia should be made. It is admitted that some of the endometria classified as late proliferative might by others be classified as hyperplasia. The number, however, would not be large enough to alter materially our results.

ENDOMETRIAL HYPERPLASIA AND FIBROID TUMORS OF THE UTERUS

In a series of publications, Witherspoon[1] has emphasized the frequency with which he has found endometrial hyperplasia an accompanying pathologic condition of fibroid tumors of the uterus. He reached the hypothetical conclusion "that the unopposed action of estrin in the absence of corpus luteum influence if prolonged sufficiently would result in fibromyomatous growths." This conclusion was largely based on a 100 per cent incidence of endometrial hyperplasia in a series of 124 uteri which contained fibroid tumors and 26 cases of endometrial hyperplasia which later developed fibroids. This constant association of endometrial hyperplasia with uterine fibroid growths was at complete variance with our general impression of its frequency. A grouping of the 727 cases of uterine fibroids according to microscopic picture of the endometrium is presented in Table I.

*Read at the Fourth Annual Meeting of the Canadian Gynaecological Travel Society, Kingston, Ontario, October 26, 1940.

TABLE I

Proliferative phase		274 cases	37.7%
Early	34 cases		
Late	240 cases		
Secretory phase		385 cases	53.0%
Premenstrual	267		
Menstrual	83		
Pregnant	35		
Hyperplasia		50 cases	6.5%
Senile		18 cases	2.4%
Total		727 cases	99.6%

The findings are about what we expected, a slightly higher incidence in the secretory phase group, due to the frequency with which hysterectomy has to be performed during menstruation and the immediate premenstrual period when fibroids are a cause of menorrhagia.

The physiologic action of estrin on the myometrium makes it a reasonable assumption that the growth of uterine fibroids, in part at least, is dependent on estrin stimulation. The age incidence of fibroid tumors, their characteristic rapid growth during pregnancy and atrophy after cessation of ovarian activity are clinical evidence of such dependency, but not evidence that disturbed estrin production is of etiologic importance in their origin. Myometrial hypertrophy is not a constant finding with uterine fibroids, and menstrual disturbances are usually gradual in onset and occur most commonly when submucous tumors are present. It is surprising how often menstruation is undisturbed even when quite large fibroids are present in the uterus. In a clinical analysis of 100 consecutive cases of complicated and uncomplicated uterine fibroids operated upon on our service, menstruation was normal in 43 cases.

In this group of 727 cases of uterine fibroids, endometrial hyperplasia, as evidence of prolonged unopposed or excessive estrin stimulation, did not occur with sufficient frequency to justify a conclusion that such a disturbance of estrin production plays any role in the origin of uterine fibroids.

HYPERPLASIA AND ENDOMETRIOSIS (EXTRAUTERINE)

Smith,[2] Jeffcoate,[3] and Witherspoon[4] have drawn attention to the frequency with which they have found endometriosis and hyperplasia as associated conditions. G. V. Smith reported 42 per cent of his cases of endometriosis complicated by "gland hypertrophy." Jeffcoate in 78 cases of external endometriosis stated "that the uterine endometrium showed hyperplasia or other features dependent on excessive estrin stimulation in all specimens examined." He concluded "that the development of endometriosis irrespective of the primary source of the endometrial elements is due to excessive estrin production by the ovaries." On the other hand, Fallas and Rosenblum[5] reported 10.7 per cent incidence of endometrial hyperplasia in 260 cases of internal and external endometriosis. We have not been impressed with the frequent

association of endometrial hyperplasia and external endometriosis. In our group of 108 specimens of endometriosis the results of microscopic examination of the endometrium of the uterine cavity were considerably different. These results are shown in Table II.

TABLE II. UTERINE ENDOMETRIAL PHASE IN 108 SPECIMENS OF EXTERNAL ENDOMETRIOSIS

Proliferative phase	34 cases	31.4%
Secretory phase	64 cases	59.2%
Hyperplasia phase	10 cases	9.2%

We have noted, however, that it is not unusual to have the ectopic endometrium fail to exhibit secretory change when the endometrium of the cavity is in the premenstrual phase. If the ectopic endometrium of endometriosis arises from serosa or germinal epithelium by heteroplasia, it is not surprising that in its varying stages of metaplasia and differentiation it shows an irregular and incomplete response to progesterone while it is dependent on estrin for its persistence and growth. The presence of a proliferative phase in such ectopic endometrium is not necessarily evidence of excessive estrin production. Endometrial hyperplasia of the uterine endometrium as evidence of prolonged or excessive estrin stimulation occurred in only 9.2 per cent of the 108 cases, an incidence not sufficiently high to warrant a conclusion that such a disturbance of estrin production is of etiologic significance in external endometriosis.

HYPERPLASIA AND UTERINE ENDOMETRIOSIS (ADENOMYOSIS)

Jeffcoate[3] in 33 specimens of adenomyoma found hyperplasia of the uterine or ectopic endometrium in 29 cases despite the fact that 21 patients were operated upon during the premenstrual period. We have noticed a high incidence of the hyperplasia pattern in the ectopic endometrium of adenomyoma. This endometrium arises from the basal layer of the endometrium of the cavity which normally is of the hyperplasia pattern. The basal layer of the endometrium frequently fails to exhibit secretory manifestations during the premenstrual phase and can be often identified in early decidua. Hyperplasia of the endometrium in the adenomyomatous areas is not, in our opinion, evidence of excessive or prolonged estrin effect. We have noted, however, a relatively high incidence of hyperplasia of the uterine mucosa in adenomyosis. The results of the examination of the endometrium in 82 specimens are shown in Table III.

TABLE III. UTERINE ENDOMETRIAL PHASE IN 82 SPECIMENS OF UTERINE ENDOMETRIOSIS

Secretory phase	39 cases	47.5%
Proliferative phase	23 cases	28.1%
Hyperplasia	20 cases	24.3%
Total	82 cases	99.9%

This 25 per cent incidence of hyperplasia is significant. The basal layer of the endometrium normally exhibits a rather uneven junction with the myometrium and frequently shows a tendency to dip down in a superficial manner between the muscle bundles. With endometrial hyperplasia it would seem reasonable to assume that this tendency might be exaggerated, even to the point of producing a typical adenomyoma.

SUMMARY

Endometrial hyperplasia of the Schroeder or "Swiss cheese type" occurred in 6.5 per cent of 727 uteri, containing one or more fibroid tumors. It occurred in 9.2 per cent of the uterine endometrium in 108 cases of external endometriosis. Endometrial hyperplasia as evidence of prolonged, excessive, or unopposed action of estrin did not occur with sufficient frequency in either group of cases to warrant a conclusion that such a disturbance of estrin production is of etiologic significance in their origin.

The occurrence of endometrial hyperplasia in the endometrium of the cavity of the uterus in 25 per cent of 82 cases of adenomyosis suggests that a disturbance of estrin production may be of etiologic importance in this condition.

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HYPOPARATHYROIDISM IN PREGNANCY, TREATED WITH DIHYDROTACHYSTEROL

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TETANY rarely occurs in the course of pregnancy, and parathyroid deficiency is usually postulated as its cause. According to Hartley,[1] "latent tetany" often occurs during pregnancy and reveals itself by paresthesias, insomnia, edema, and cramplike pains in the legs and thighs. Both tetany and "latent tetany," as Shelling[2] has aptly stated, may not be due to parathyroid insufficiency, but to several other factors, "such as the calcium and phosphorous, and vitamin D intake, and the calcium and phosphorous storage." Although 54 cases of tetany in pregnancy could be found in the literature, in only one case was the tetany preceded by an operation in which the parathyroids had been removed or damaged. This case was reported by Baumgartner and Cowles.[3] The tetany followed two months after a subtotal thyroidectomy for hyperthyroidism. The patient was treated with calcium, cod-liver oil, and parathormone, but later the parathormone was discontinued. She subsequently delivered a normal term infant. The writers wish to report a similar case. Our patient, however, was carried through her pregnancy with the help of dihydro-

tachysterol (A.T.10*). To our knowledge, she was the first pregnant woman so treated. A detailed account of this case prior to the pregnancy has been reported by J. K. Curtis.[4]

Chemically, A.T.10 is a derivative of irradiated ergosterin. The fraction, tachysterin, is converted to dihydrotachysterol to make it suitable for administration by mouth. This drug is potent in increasing calcium absorption from the intestines and raising the blood calcium level. It has been found very useful in managing cases of hypoparathyroidism.

CASE REPORT

The patient, B. M., a 15-year-old schoolgirl was first seen at the First Surgical Division of Bellevue Hospital in March, 1931. She had typical signs and symptoms of hyperthyroidism. After the usual preparation a subtotal thyroidectomy was performed. The patient improved, but after a few months there was a recurrence of her old complaints. Another partial thyroidectomy was performed, and she was again discharged improved.

The patient then married. In 1936 she was delivered of a normal full-term infant without difficulty. In spite of taking iodine intermittently she returned to the hospital in 1937 with a recurrence of her symptoms of hyperthyroidism. A third partial thyroidectomy was performed. No parathyroid tissue was noted grossly or microscopically in the removed specimen.

Two days postoperatively the patient complained of stiffness in the fingers and muscle cramps. Chvostek and Trousseau's signs were present. She received all the usual forms of treatment of tetany, including high calcium, low phosphorus, and ketogenic diets; calcium orally and intravenously; viosterol and parathormone. In spite of this therapy she had several severe convulsions. In April, 1937, four months after her last operation, blood partition showed: calcium, 5.7 mg. per cent; inorganic phosphorus, 5.5 mg. per cent; serum phosphatase, 3.1 Bodansky units; nonprotein nitrogen, 28 mg. per cent; total protein, 8; albumin, 4.8; globulin, 3.2; euglobulin, 0.7. A year later blood calcium was 4.8; phosphorus, 5.8 (see Table I).

The patient went one year and nine months in a profound degree of parathyroid insufficiency, unrelieved by the customary forms of therapy. At this point antitetanic 10 was given, the patient receiving 1 c.c., along with 2 teaspoonfuls of calcium lactate and 20 drops of viosterol daily. In a week she was much improved. She gained weight, had no complaints, and Chvostek and Trousseau's signs were absent. In April, 1939, blood calcium was 9.9; phosphorus, 4.6. Since the blood

TABLE I. SHOWS WEIGHT, BLOOD CHEMISTRY DETERMINATIONS, AND THERAPY IN A PATIENT WITH HYPOPARATHYROIDISM BEFORE PREGNANCY

DATE	WEIGHT POUNDS	MEDICATION			BLOOD CHEMISTRY			
		CA. LACTATE GR.	VIOSTEROL GTT.	A.T.10 C.C.	CA.	P.	PHOSPHATASE	N.P.N.
4/19/37	122	25	30		5.7	5.5	3.1	28
3/30/38	115½	25	30					
10/19/38	110¼	10	20	1.0	4.8	5.8		
11/ 2/38	112	10	20	1.0				
11/ 9/38	113½	10	20	1.0				
11/23/38	114½	10	20	1.0				
12/21/38		10	20	1.0	7.0			
3/ 1/39	115¾	10	20	1.0	9.9	4.6	0.9	33
4/18/39	117½	10	20					
5/ 3/ 39	116	10	20	1.0	5.5	5.6		
5/31/39	115	10	20	0.5				

*Abbreviation for "anti-tetanic 10," prepared by Winthrop Chemical Co., N. Y.

calcium was now normal, the anti-tetanic 10 was discontinued in the hope that a normal calcium level could be maintained by giving only calcium lactate and viosterol. The blood calcium, however, promptly dropped, and her old complaints returned. Her symptoms again disappeared after receiving antitetanic 10. Her maintenance dose appeared to be 1 c.c. daily, and she continued to receive this amount (see Table I).

When seen in October, 1939, at the Bellevue Obstetrical Clinic, she was two and one-half months pregnant. Therapeutic abortion was considered, but because of her good general physical condition and intense desire for another child, the pregnancy was not interrupted. The blood calcium was taken at frequent intervals, and she was closely followed throughout her pregnancy. In order to maintain a normal blood calcium, the maintenance dose of anti-tetanic 10 was gradually increased from 1 c.c. daily to 1 c.c. t.i.d. She also received 15 gr. of calcium lactate t.i.d. and 10 minims of viosterol b.i.d. (see Table II). The patient felt well throughout her pregnancy and offered no complaints.

TABLE II. SHOWS WEIGHT, BLOOD CHEMISTRY DETERMINATIONS, AND THERAPY IN A PATIENT WITH HYPOPARATHYROIDISM DURING HER PREGNANCY AND PUERPERIUM

DATE	WEIGHT POUNDS	MEDICATION			BLOOD CHEMISTRY			
		CA. LACTATE GR.	VIOSTEROL GTT.	A.T.10 C.C.	CA.	P.	PHOSPHATASE	N.P.N.
9/27/39	117½	10	10 o.d.	2	6.2	5.4		
10/18/39	114½	10	10 o.d.	1	8.5	4.3		
11/22/39	116¾	10	20 o.d.	2				
12/13/39	118½	30	20 o.d.	3				
12/20/39	120	45	20 b.i.d.	3				
1/ 3/40	121¼	45	20 b.i.d.	3				
1/10/40	122½	45	20 b.i.d.	3	9.8			
1/24/40	123½	45	20 b.i.d.	3				
2/ 7/40	125¾	45	20 b.i.d.	3				
2/21/40	126½	45	20 b.i.d.	3				
3/ 6/40	128¾	45	20 b.i.d.	3				
3/20/40	128	45	20 b.i.d.	3	9.1	4.1		27
4/ 3/40	130	45	20 b.i.d.	3				
4/17/40	133	45	20 b.i.d.	3	9.4	4.6	7.0	36
5/ 1/40	138	45	20 b.i.d.	3				
5/15/40	134	45	20 b.i.d.	3	9.0		9.0	29
5/29/40		15 gr. calcium gluconate I V						
		Birth of Infant						
6/ 3/40		30	15 b.i.d.	2	10.7		4.6	
7/ 3/40	116½	15	10 b.i.d.	½				
7/31/40	113½	15	10 b.i.d.	½				
9/18/40	112	15	10 b.i.d.	½				

She was admitted to the obstetric ward at midnight of May 29, 1940. Labor pains had started a few hours before admission. The patient was now in active labor. A slightly oversized full-term infant was presenting by the breech, which was at the level of the spines. The cervix was fully dilated. Physical examination was otherwise essentially negative. Soon after admission the infant was easily delivered as an assisted breech and was an apparently normal female child, weighing 8 pounds and measuring 20 inches in length. The third stage of labor was uneventful, and immediately following this the patient received 10 c.c. of 10 per cent calcium gluconate intravenously. Both mother and infant were returned to the ward in good condition. She ran a non-morbid, uneventful post-partum course. She was not allowed to nurse the infant. On the fourth post-partum day, because the blood

calcium was a little high (10.7 mg. per cent), the dosage of anti-tetanic 10 was reduced from 1 c.c. t.i.d. to 1 c.c. b.i.d. daily (see Table II). The puerperium was non-morbid and uneventful. On the tenth post-partum day she was sterilized by the technique of Pomeroy through a small abdominal incision. The postoperative course was smooth. The patient was discharged with her infant on the twenty-second post-partum and thirteenth postoperative day, both in good condition. X-ray of the long bones of both mother and infant showed no abnormalities.

SUMMARY

A case is reported of chronic parathyroidism following a subtotal thyroidectomy, in which the blood calcium was maintained at normal levels by the use of anti-tetanic 10 (dihydrotachysterol) along with calcium and viosterol. The patient subsequently became pregnant. The pregnancy, delivery, and puerperium were uneventful. To our knowledge, this is the only pregnancy in which anti-tetanic 10 has been used.

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ADEQUATE TRANSVAGINAL DRAINAGE OF THE PELVIS

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THE technique for excision of diseased female generative organs has been constantly improved, yet methods for draining the pelvis after operation have not kept pace with these advances. The common causes of morbidity and mortality following hysterectomy are complications arising in the pelvic peritoneal cavity. The most frequent complications are peritonitis, abscess, hematoma, and intestinal obstruction. Inadequate postoperative drainage of the pelvis is the factor which precedes and predisposes to these unfortunate post-operative conditions.

Gynecologists, in general, acknowledge the highest mortality from panhysterectomy, a lower mortality from supravaginal hysterectomy, and the lowest mortality from vaginal hysterectomy.[1-5] It does not seem rational that the majority of operators should prefer the abdominal approach for excision of the uterus when the lowest mortality is obtained from transvaginal operations, yet this is apparently the case. There is one striking difference in the various techniques for excision of the uterus which accounts for the minimum mortality rate from vaginal hysterectomy. This is the excellent facility for release of bloody serum from the pelvis through a vent in the vaginal vault after operation. Strangely enough, vaginal hysterectomy which reports the lowest mortality rate also reports the highest morbidity rate.[1, 5, 6] The obvious reason for this is failure to obtain adequate drainage through the vaginal vault after operation.

The most frequent cause of death following hysterectomy is peritonitis.[1, 2, 5, 7] If the peritoneal cavity can be adequately drained of the free fluid which forms after operation, spreading peritonitis can be largely prevented, because peritonitis spreads by means of a liquid medium. Bloody serum which collects in the pelvis after hysterectomy acts as an ideal pabulum for pathogenic bacteria introduced at the time of operation. True, our aseptic methods for the abdominal operation will hold contamination at a minimum, but in transvaginal operations the contamination is undoubtedly much greater, since the cervix and vaginal mucosa cannot be made sterile. Patients who are not required to absorb either sterile or septic fluid from the peritoneal cavity after operation will have a lower morbidity and mortality rate, a lower incidence of postoperative ileus, a smoother convalescence, and a shorter hospitalization period.

Rubber or gauze should not be placed in the peritoneal cavity when free drainage is desired. Laboratory and clinical observations have shown that these substances produce a marked local irritation of the peritoneum.[8] This results in a rapid fibroplastic exudative incapsulation of the rubber and gauze. Within six to eight hours the reaction of the peritoneum to rubber or gauze converts these drains into mechanical corks which actually impede the escape of septic fluids and are effectual in draining only the limited tissue space which they irritate. Drains made of inorganic materials such as glass or stainless steel produce little or no irritation of the peritoneum and, therefore, afford a satisfactory material for obtaining prolonged and adequate drainage.

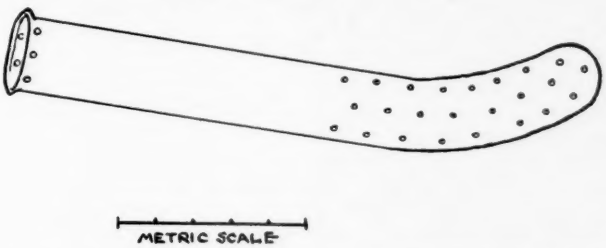

Fig. 1.—Pyrex glass tube which is inserted into the pelvis through the vaginal vault to drain the peritoneal cavity for three days following hysterectomy.

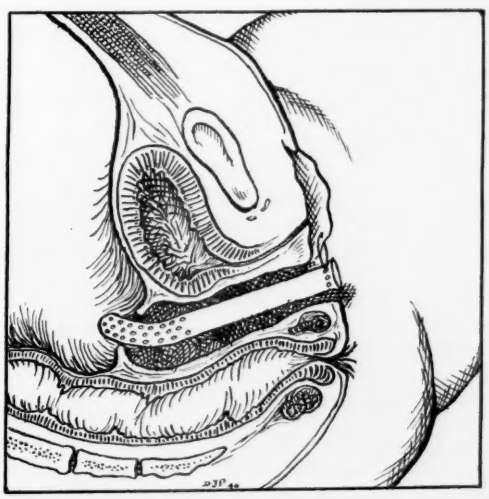

Fig. 2.—Diagram in the sagittal plane, showing position of glass tube for prolonged gravity drainage of the pelvis after excision of the uterus. Gauze or rubber inserted into the pelvis prevents adequate free drainage.

By substituting a non-irritating drain made of inorganic material for the gauze or rubber drains commonly in use, one can obtain free drainage from the pelvis after vaginal hysterectomy. It is ineffectual and dangerous to leave an unprotected opening in the vaginal vault after operation, as the hole would be quickly plugged by an intestinal loop and lead to the possibility of intestinal herniation. A suitable glass tube (Fig. 1) introduced into the pelvis prevents hernia and maintains prolonged open drainage. This type of tube is made of pyrex glass and can be constructed according to specifications by a glass blower. It may be curved to conform to the shape of the pelvic passage. The end which is inserted into the pelvis is rounded and closed but contains multiple small perforations 1 to 2 mm. in diameter. The external end is open and may be anchored to the labia by a suture through one of the small holes along the rim.

Any technique for excision of the uterus may be employed, but the opening in the vaginal vault after vaginal hysterectomy should then be partly closed to leave a fenestration of appropriate diameter to fit around the glass tube. The vaginal walls are protected from pressure of the glass drain by a strip of plain gauze packing which is moistened with saline and inserted loosely around the tube from the vaginal vault to the entroitus. No gauze is introduced into the pelvic opening (Fig. 2). The drainage of serous fluid is frequently so profuse during the first and second postoperative days that the perineal pads become saturated and wet the bedding unless replaced every few hours. I do not know of any convenient method for estimating the amount of drainage in these cases, but to even the casual observer there is considerably more fluid from the glass tube drain than is seen when gauze or rubber drains are used.

Drainage is usually scanty by the third postoperative day, and it has been routine to remove the glass tube at that time. The patient is placed on an examining table, the vaginal gauze packing gently withdrawn, the anchoring suture cut, and the glass tube which does not stick to the tissues is easily slipped out. A bivalve speculum is then inserted and a view through the opening in the vault reveals a normal glistening peritoneum without exudate or adhesions. With the speculum in place, the vagina is again loosely packed with saline moistened gauze from vault to entroitus. Gauze is never introduced through the opening into the pelvis.

Vaginal packing is removed without difficulty on the fifth or sixth postoperative day. By this time the opening into the pelvis is already sealed off and healing progresses rapidly. The patient is permitted out of bed on the seventh to ninth day after operation.

This procedure for pelvic drainage has been employed in a small series of vaginal hysterectomies. Technique of excision was the serial suture-ligation and division of vessels without clamps.[9] Annealed stainless steel wire was used for all ligatures and sutures in preference to catgut or silk which produce unfavorable foreign protein reactions in tissue.[10]

Table I summarizes the data on fifteen consecutive hysterectomies treated with the transvaginal pelvic glass tube drain. Indications for operation were procidentia uteri, fibrosis uteri, and fibroid tumors. One-third of the patients had large tumor masses palpable by abdominal examination. These varied in size up to the dimensions of a five months' pregnancy and required morcellation for removal. Nearly

TABLE I. SUMMARY OF 15 CONSECUTIVE VAGINAL HYSTERECTOMIES TREATED WITH THE TRANSVAGINAL GLASS TUBE DRAIN

Age range	27-63 years
Average age	42 years
Anesthesia:	
Spinal	93%
Local	7%
Excision by morcellation	33%
Other operations + hysterectomy	46%
Average postoperative days in hospital	10 days
Postoperative morbidity	Pyelitis, 1 case

one-half of the group underwent other operations at the time of hysterectomy, including oophorectomy, salpingectomy, posterior colpoperineoplasty, and repair of abdominal incisional hernia. One patient developed a transient pyelitis after operation. This was the only case with postoperative morbidity and none of the others had a temperature above 100.6° F. for any twenty-four-hour period. All of the patients were comfortable after operation and none complained of discomfort from the glass drainage tube. One patient, 27 years old, who was operated for third degree procidentia uteri with a two months' pregnancy and recurrent uterine hemorrhages, was allowed out of bed on the fifth day after operation and returned home on the sixth day in good condition. Although there was no

apparent harm from her early return to activity, it would seem wise to keep these patients in bed for at least seven days. The average postoperative period of convalescence in the hospital for this group was ten days.

It is not the purpose of this article to advocate vaginal hysterectomy as being better than operations done through an abdominal incision. However, it is the purpose here to indicate the advantages of glass tube gravity drainage of the pelvis following excision of the uterus. It is rational to believe that the higher death rate from supravaginal hysterectomy could be reduced to a figure approaching the present mortality rate for vaginal hysterectomy if the principles of adequate pelvic drainage were applied. For this reason it is suggested that following the abdominal closure in supravaginal hysterectomy, the patient should be draped in the lithotomy position, an opening made in the posterior vaginal cul-de-sac and a transvaginal glass tube drain inserted into the pelvis to complete the operation. This will afford prolonged free gravity drainage which cannot be secured with gauze or rubber drains whether they be inserted through an abdominal incision or through the vaginal cul-de-sac. The disability and death from peritonitis, abscess, hematoma, and intestinal obstruction can be largely prevented if adequate drainage of the pelvis is maintained during the early days after hysterectomy. Although the method here described has been used for only a short time, the favorable results obtained indicate that further use of this new technique for drainage is warranted.

SUMMARY

The advantages of the transvaginal glass tube pelvic drain following hysterectomy are:

1. The special glass tube affords adequate and prolonged gravity drainage of the pelvic peritoneal cavity which cannot be obtained by the use of gauze or rubber drains.

2. Septic or spreading peritonitis is prevented by removal of all free fluid from the pelvis which may act as a culture medium for bacteria and a vector for transmitting infection into the abdominal cavity.

3. Intestinal obstruction after operation is prevented by free drainage through the glass tube of septic materials which result in plastic exudate and peritoneal adhesions. Gauze and rubber, because of their organic composition, produce irritation resulting in fibroplastic exudate and should not be introduced into the peritoneal cavity.

4. Immediate recognition of secondary hemorrhage after hysterectomy may be lifesaving. Hemorrhage from a slipping ligature becomes apparent at once, since the open glass drain gives rapid egress for blood from the pelvis and thereby prevents unrecognized hemoperitoneum.

5. The glass drain does not stick to the tissues and can be removed easily without trauma. Foreign body irritation of the peritoneum is reduced to a minimum, since the inorganic glass tube produces little or no tissue reaction.

6. Reduction of postoperative morbidity from intrapelvic complications results in a shorter period of hospitalization. Adequate prolonged drainage of the pelvis from the time of operation prevents the formation of abscess and hematoma.

7. Excision of the uterus by any technique or method does not preclude the use of the transvaginal glass tube drain, nor does this tube interdict vaginal plastic or perineal operations in conjunction with hysterectomy.

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BILATERAL GRANULOSA CELL TUMORS*

Successful Removal From a Child Fourteen Weeks of Age

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INTEREST in solid ovarian tumors has been greatly stimulated in the past few years as a result of correlation between the known histologic structure of such tumors and the more modern methods of identifying their hormonal content. To Rokitansky perhaps belongs the credit for first describing a tumor composed mainly of large and small follicular structures surrounding protoplasmic disks filled with granular bodies. Pathologists who amplified his description were Acconci, von Kahlden, Schroeder, Werdt, and Meyer.

In spite of much investigation, little is known of the origin of these tumors. Among the many concepts is that of Meyer, who felt that the tumors arose from cell rests in the ovarian hilus. Recent experiments of Butterworth have tended to show that the growths might be produced experimentally as a result of roentgen therapy. If this concept is sustained, an intimate relationship between the development of such tumors and the application of roentgen therapy to women may be established. The evidence for such a relationship, however, is as yet inconclusive.

Robinson, in 1923, was the first to publish in the American literature a report of a case of granulosa cell tumor. King, in 1929, reported 2 cases, and since 1930 the number of reports of cases has increased to considerably more than 400. Among the prominent contributors to the subject might be mentioned Novak, Long, TeLinde, Frank, Schulze and Neumann. One of the most comprehensive reviews of the subject of granulosa cell tumors was reported in 1935 by Bland and Goldstein. At that time 160 cases of this type of tumor were recorded. In 1939, Dockerty and MacCarty added 30 cases from material gathered at the Clinic from 1905 to 1937.

Study of the data on granulosa cell tumors so far reported brings out certain definite clinical characteristics of this tumor. Sixty per cent of granulosa cell tumors occur after the menopause and 30 per cent between puberty and the climacteric, whereas only 5 to 10 per cent occur before adolescence. The relatively infrequent occurrence of this type of tumor before adolescence is indicated by the fact that only eight tumors occurred among patients less than twelve years of age in the series of 160 reports of cases collected by Bland and Goldstein. The respective ages of these patients, in years, was 5, 9, 5, 11½, 4, 5, 6, and 7. The youngest patient represented in the foregoing series, and probably in the literature up to the time of writing the present article, was 4 years of age; the case was reported by Novak. The matter of age is of some significance, since we believe our patient to be the youngest individual in relation to whom a granulosa cell tumor has been diagnosed and from whom such a tumor has been successfully removed. The tumors in this case were bilateral, although such tumors occur bilaterally in less than 5 per cent of cases. When, therefore, the fact is considered that only 20 per cent of all ovarian tumors are solid and that of these only 10 per cent are granulosa cell tumors, this case becomes almost a medical curiosity.

In childhood it is not uncommon for precocious menstruation, together with early sexual and somatic development, to be a symptom of these tumors. However, these need not be leading symptoms. Additional presenting symptoms may include abdominal tumor, abdominal pain, ascites, or hypertrichosis. The tumor may even be discovered accidentally. The present case is further interesting, since the only suggestion of the presence of disease was abdominal tumor.

*Submitted for publication, November 12, 1940.

REPORT OF CASE

A white American girl was born uneventfully, at full term, April 1, 1937. The mother had had one child previously. The birth weight of the child was 8 pounds 13 ounces (4 kg.). Her early progress was satisfactory except that she did not gain weight normally. On May 19, when the child was examined because of a feeding problem, her weight was 10 pounds (4.5 kg.); she had gained only 1 pound 3 ounces (0.6 kg.) since birth. Alteration in the child's formula was prescribed. She was seen again on June 1, at which time she had gained only 1½ ounces (45 Gm.) more than the weight noted on the visit on May 19, in spite of what might be considered an increase in feeding.

Fig. 1.—Bilateral granulosa cell tumors: *a*, tumor from right side, 5 by 5 by 4 cm.; *b*, tumor from left side, 3 by 2.5 by 2 cm.; *c*, cut surface of the larger tumor.

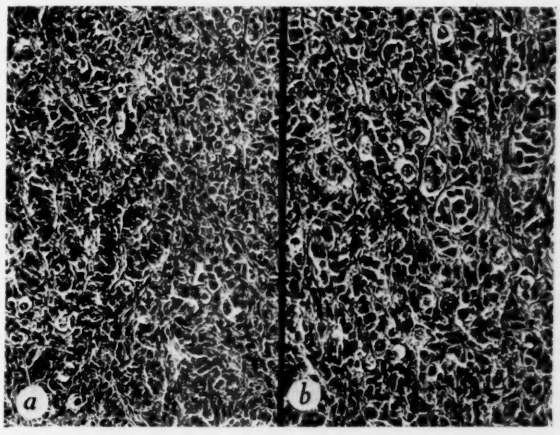

Fig. 2.—Different section of tumor stained with hematoxylin and eosin: *a*, cylindroid and diffuse cellular pattern (×140); *b*, folliculoid cellular pattern (×200).

The child was seen once more on July 9. She was then fourteen weeks of age and her weight was 10 pounds 10 ounces (4.8 kg.), which represents a gain over the original birth weight of only 1 pound 13 ounces (almost 1 kg.). At this time, a mass was found in the lower right abdominal quadrant. This mass, which was the size of a large lemon, had not been present when previous examinations had been made. The remainder of the examination did not disclose anything abnormal. Consultation was then sought concerning the tumor. The diagnosis entertained by all the consulting physicians was a malignant growth involving either a kidney or an ovary, and the prognosis was considered grave.

In spite of the diagnosis of abdominal malignancy, exploration was made by one of us (Zemke) on July 23, with the patient under ether anesthesia. The child was then sixteen weeks of age. Bilateral, solid ovarian tumors were found (Fig. 1 *a*, *b*, and *c*). The uterus was considered to be of average infantile size although it may have been slightly enlarged. Bilateral oophorectomy was performed, leaving the uterus and other adnexa intact. The wound was closed in the usual manner. Postoperative convalescence was uneventful and the girl was dismissed from the hospital on the seventh postoperative day.

From that time onward, the child made what might be considered normal progress. She was seen at intervals of about three months. Eleven months from the time of operation the child's weight was 23 pounds 9 ounces (10.7 kg.), which represents a gain of approximately 13 pounds (almost 6 kg.) in less than a year.

Up to this time, the child herself had not been seen by a physician of the Mayo Clinic, but in May, 1940, one of us (Herrell), in informal conversation concerning the case, suspected the growths of being granulosa cell tumors and, a few days later, was able to confirm the suspicion by gross and microscopic examination of the tissue. Characteristic cells, with large basophilic nuclei, constituted the predominant cellular structure. The structural unit also was characteristically cylindroid with transitions to the folliculoid type (Fig. 2 *a* and *b*). Grossly, both tumors were well

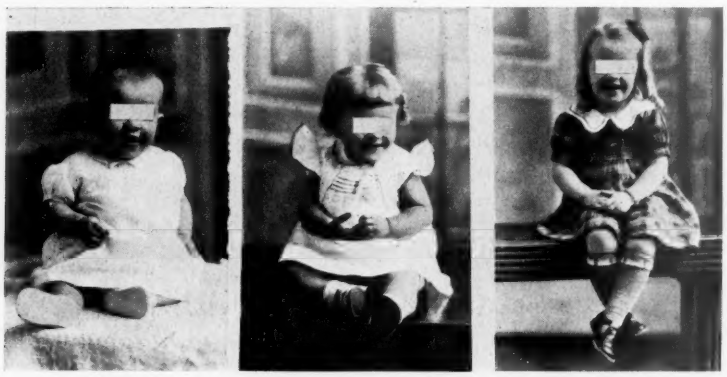

Fig. 3.—Appearance of patient. Ages from left to right: seven and one-half, sixteen, and thirty-three months.

encapsulated; their surfaces were smooth and grayish brown. On section, the masses were solid throughout and were of homogeneous, granular texture. The diagnosis of granulosa cell tumor was further confirmed by Dockerty of the Mayo Foundation of the University of Minnesota, at Rochester, and it was subsequently learned that Bell, of the same university, in Minneapolis, in the light of the subsequent clinical course, had suspected the true nature of the tumors.

The child's growth and development were entirely within normal limits and, at the time of writing this report, she had been followed for three years and two months (thirty-eight months) (Fig. 3). When last seen Sept. 1, 1940, she enjoyed perfect health. Her height at that time was 37 inches (93.94 cm.) and her weight, 33 pounds (15.0 kg.).

Endometrial studies were not possible and, unfortunately, studies with relation to urinary or blood hormonal content were not available. The specimens also were preserved in formalin, which precluded their study from the standpoint of hormonal content.

SUMMARY

Bilateral tumors of the ovaries were discovered when the child was fourteen weeks of age, and the tumors were successfully removed when she was sixteen weeks of age. Two years and eight months later these tumors were determined to be

granulosa cell tumors. The patient seems to be the youngest yet to be reported to have had this disease. When this report was written, three years and two months subsequent to operation, the girl was apparently well. The case is one of that small group (5 to 10 per cent) of cases in which the condition occurs before puberty. It is further unique in that the tumors were bilateral; bilaterality occurs in not more than 5 per cent of all cases of granulosa cell tumor.

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CASE OF DIPROSOPUS TETRANOPHTHALMOS

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DIPROSOPUS is a term applied to a fetal monster having two faces but with close union of the heads and bodies throughout. It is a rare teratism in man, being considerably more common in lower animals, especially the cow and cat. The duplication is not limited to the head but, as clearly shown in radiographic studies, includes the trunk as well. The double spinal column at times is well marked as far down as the sacrum, according to Dorland and Hubney's[1] *The X-ray in Embryology and Obstetrics.* Unlike most of the cases reported, which are of the triophthalmic type, my case is one of tetranophthalmia. It is of interest not only because of its rarity, but because roentgenographic studies of the monster in utero were obtained, thus leading to a prepartum diagnosis of monster and preparing the family to expect a malformed, nonviable child.

The etiology of the condition is not known. It is either a splitting of a primitive stick or the fusion of two primarily developed ones, the former being the more tenable theory. This report will not touch upon the classification of double monsters, as any good textbook on obstetrics includes these interesting and rare studies.

In 1921, Beach[2] reported a case of derodidymus (dicephalus) with a review of some of the cases which had occurred prior to his report. His case was in a normal female, aged 29 years. After difficult manipulation lasting forty-five minutes, the patient was delivered of the monster. The specimen was of the dicephalic type with two vertebral columns joining the one sacrum.

Also in 1921, Cibelius[3] reported a case of dicephalus with two complete spines. His case was a secundipara, aged 20 years. The delivery was difficult, a breech, with simultaneous delivery of the two heads. Study of the case revealed two hearts, two aortic arches, two superior vena cavas, two inferior vena cavas, and two thoracic aortas. The abdominal findings were indistinct.

Gaddie and Sims,[4] in 1929, reported a case of anacatadidymus. Their case, a septipara, aged 35 years, was a spontaneous delivery, the monster weighing eleven pounds. One skull was of normal size and the other about two-thirds normal. Their report contains minute detail of roentgenographic and necropsy examinations of the interesting specimen.

Grant,[5] in 1921, reviewed the classification of double monsters and reported a case. The mother was a primipara, aged 28 years. The delivery was difficult but spontaneous. X-ray study revealed a dicephalic monster with double spine and a clavicle between the two heads.

In 1926, Ivens and Edgecombe[6] reported a case of dicephalus dibroachius dipus causing obstructed labor. The specimen was a double-headed monster weighing about seven pounds. There were two heads, two arms, two legs, and a single body which had two distinct spinal columns, approximating in the sacral region.

Mandruzzato,[7] in 1932, published a detailed article on the embryogenesis of anencephalia and spina bifida. This article is included in the review of cases because of his studies of spina bifida, an anomaly in the case being reported.

Rose,[8] Morrison,[9] and Mitchell[10] in 1927, reported three dicephalic monsters. The first was a dicephalic fetus with apparently normal body. The second was a similar case, both of which were exceedingly difficult deliveries. The third case was of a different type, being a syncephalus thoracopagus. There were four arms and four legs, the bodies being united at the thorax.

In 1931, Shortall[11] reported a case of double monster occurring in a secundipara, aged 33 years. Examination of the specimen disclosed two female fetuses fused at the pelvis, anteriorly. Radiologic examination revealed a fusion of the lumbosacral region of the vertebral columns with absence of one sacrum.

Mudaliar,[12] in 1931, reviewed double monsters in an extensive study of their circulatory system and some other anatomic abnormalities and the complications in labor. His radiographic studies and drawings are most complete and enlightening to one interested in these embryologic anomalies.

REPORT OF AUTHOR'S CASE

The patient, a secundipara, was 28 years of age. Her previous pregnancy was a normal one at the age of 25. Her prepartum course in the first pregnancy was normal in every respect. The baby, a female, weighed 8 pounds 1 ounce at birth and the delivery was spontaneous. Her post-partum course was entirely normal and satisfactory.

She presented herself to her physician with this pregnancy when she had missed her second period. Her routine physical examination at that time was negative except for some tenderness under the right costal margin in the region of the gall bladder. She was given routine prenatal care every three weeks, i.e., urinalysis, weight, blood pressure, and fundal measurement. When she was about six and one-half months pregnant, it was noted that there had been a sudden rise in the fundal measurement and the fetal heart could no longer be heard. It was impossible to palpate fetal outlines so a diagnosis of polyhydramnios was made. In view of the fact that there was a possibility of multiple pregnancy or monster, a routine x-ray study of the patient was advised. This was performed at the seventh month, at which time her fundal measurement had risen to 33 cm. (term size). The roentgenologist's report on that study, done on May 14, 1940, by George U. Pillmore, M.D., Roentgenologist at the Easton Hospital, follows:

Roentgenologist's Report.—"The x-ray examination of the abdomen discloses a teratologic specimen of the anencephalic type developed well along toward full term. There is a mid curvature of the spine, and it is noted that the rib spacing is rather close together on one side. Possibilities exist as to the presence of an extra vertebra causing the distortion of the spine or it may be because of collapse of the chest commonly seen at fetal death. Request the privilege of x-ray and photographing specimen after delivery."

When the report was studied by the roentgenologist and myself, the family was advised that the child would be a nonviable monster, and they were advised that the pregnancy would best be allowed to terminate spontaneously.

During the next month, the fundal measurement rose to 39 cm. and the patient was most uncomfortable. There were no audible fetal heart sounds although the patient felt fetal movements. Rectal examination disclosed no presenting part.

When she was about eight months' pregnant, her membranes ruptured suddenly at home and she discharged a large amount of amniotic fluid. In the interval between the time she called her physician and his arrival she weighed herself and

found she weighed thirteen pounds less since the membranes had ruptured, an indication of the excessive amount of amniotic fluid. She was taken to the hospital at once.

The labor was comparatively long, 28½ hours. The delivery was spontaneous, a vertex presentation, which presented no particular difficulty under nembutal and scopolamine analgesia and gas oxygen anesthesia. The fetus was stillborn but not macerated. The puerperium was satisfactory and the patient was discharged from the hospital on her tenth post-partum day.

The fetus itself was a well-formed female, weighing exactly five pounds and was 19½ inches in length. It was essentially normal in appearance anteriorly except for the face (Fig. 1). Two complete faces were present with fusion of the ears in the center. Posteriorly there was a wide area, some four inches across,

Fig. 1.

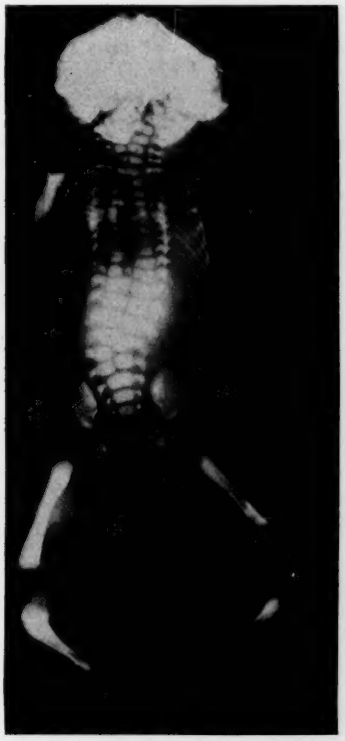

Fig. 2.

of the bifid spine which extends from the lower thoracic area to the occiput where it broadened into a bloody mass in the occiput itself composed of brain tissue covered by the meninges. Necropsy was not performed because I wished to preserve the specimen intact for museum purposes. The x-ray study of the fetus follows (Fig. 2):

Roentgenologist's Report on the Specimen.—"The x-ray examination of the monster discloses a diprosopus tetranophthalmos. The diprosopus specimen demonstrates two well-developed lower mandibles with the dental buds in each lower mandible well arranged. The lower right side of one frontal is fused with the left side of the opposite fetal frontal. Four orbits are well formed. There are two separate sets of cervical vertebrae extending up into the individual skull bases. There is fusion of the spine at the first dorsal. Below this, there are two separate spines until the fifth lumbar is reached, where there is fusion and an accessory vertebra on the right side. Both clavicles, scapulas, and the bones of each arm are

well formed. The same is true for the bones of the pelvis and each lower extremity. There are twelve ribs on each side in perfect development in the anterior-posterior view, but in the lateral view, there is a marked kyphosis of the lower dorsals. This had distorted the position of the ribs posteriorly so that their attachments to the spine on each side are at acute angulation. The specimen, from the radiological standpoint, is considered to be an unusually rare one.''

Postnatal Review of ''In Utero'' Films.—''In reviewing the films of the monster in utero, it is impossible to outline the double faces of the specimen. In the anterior-posterior view of the abdomen, the skull was superimposed upon the maternal pelvis. The lateral view demonstrated only the superimposition of the two faces. The kyphosis of the specimen was clearly demonstrable.''

SUMMARY

1. An unusual and rare case of fetal monstrosity is reported.
2. I have been unable to find a similar one in the literature at my disposal.
3. An interesting comparison is shown between the pre- and postnatal roentgenologic studies of the case.

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RECESSION OF TOXEMIA FOLLOWING THE INTRAUTERINE DEATH OF ONE OF DIZYGOTIC TWINS

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WE HAVE been urged to report the following case because of its interest and any possible light it may throw on the etiology and pathologic physiology of eclampsia. We purposely refrain from drawing any implications or interpretations of our own.

Mrs. I. A., a Jewish primipara, aged 34 years, presented herself for prenatal care at the end of her seventh week of pregnancy. She had been married two months. Her last catamenia started July 7, 1939, making her estimated date of confinement, April 13, 1940.

Her past history was negative. She complained chiefly of an almost continual nausea and vomiting, in spite of which she had gained six pounds over her original weight of 125. Blood pressure was 110/70. Urine and Wassermann examinations were negative.

The patient was seen one month later, during which time she had a two weeks' illness with severe upper respiratory infection. Routine physical examinations revealed essentially negative findings. Head, throat, teeth, heart, lungs, abdomen, and extremities were normal. The uterus was 2.5 cm. above the pubis. Pelvimetry showed: intercristal diameter 28 cm., interspinous 20 cm., external conjugate 20 cm., and transverse outlet 10 cm. The sacral promontory could not be felt.

Subsequent monthly office visits showed no abnormalities until the twenty-eighth week, Jan. 18, 1940, when it was noted that the blood pressure was 140/90 and weight 151 pounds. Edema of the feet and ankles and albuminuria did not appear until the thirty-third week.

Expectant treatment with rest, limitation of fluid intake, salt-free diet, and increased elimination was instituted. The patient was seen at weekly intervals, and the signs and symptoms of toxemia progressed. By March 10, the thirty-sixth week, the hands and face were markedly puffy, the urine was heavily loaded with albumin, and the blood pressure reached 150/100. Her weight was now 160 pounds.

Ten days later, to our amazement, the albuminuria and edema had disappeared. The blood pressure was still elevated. The cervix was effaced, thin, and 2.5 cm. dilated. The baby was active, and the fetal heart was distinctly audible in the left lower quadrant. We were at a loss to explain this sudden clinical improvement.

When seen a week subsequently, March 27, the blood pressure was 144/90, and she was free of albumin and edema. Her weight was 152 pounds.

Labor began spontaneously, April 1, 1940, two weeks before the estimated date of term. She was admitted to the Massachusetts Women's Hospital and after four and one-fourth hours of labor she was delivered normally of a female child, L.O.A. position, weighing 5 pounds 8 ounces. The baby was normal in every way. Six minutes later a second fetus, male, macerated, stillborn, R.S.A. position, weighing 3 pounds 5 ounces, was extracted. The extent of maceration was deemed to coincide with the duration of clinical recession of the toxemia. The placentas were expressed five minutes later. They were fused and platter shaped.

The mother and live baby progressed uneventfully and were discharged from the hospital on the seventeenth day post partum.

PATHOLOGIC REPORT (DR. J. STEWART ROONEY)

Gross Examination.—Specimen of double ovum, fused, twin placentas weighing 630 Gm. and measuring 19 cm. across the septum. One placenta measured 12 cm. in diameter, while the other measured 17 cm. One cord was marginally attached, measuring 40 by 1 cm., while the other cord was attached 3 cm. from the margin and measured 40 by 1 cm. There was no anastomosis of the vessels. The membranes (the septum) consisted, in succession, of amnion, chorion, chorion, and amnion. The fetal surface was slightly meconium stained and suggested maceration. The material surface was pale. A cut across the septum showed a marginal area of yellow, granular, ischemic necrosis on the smaller side which looked diffusely avascular compared to the larger side.

Microscopic Examination.—Sections through the avascular placenta showed a marginal area of ischemic necrosis, with necrosis of the underlying decidua. Elsewhere the decidua showed the characteristic moth-eaten and fibrinoid degeneration. The chorionic villi were slightly immature in size and shape and showed slight necrosis of the stroma. The surface syncytium showed fewer knots than in maturity. The larger vessels of the main-stem villi and chorionic plate contained moderate numbers of red cells, but the villi were otherwise avascular, and there was almost no blood in the intervillous spaces. A second section through the septum between the two placentas showed the avascular placenta as described above. The vascular placenta showed slight immaturity of the chorionic villi, but the vessels were filled with red cells and there were moderate numbers of red cells in the intervillous spaces. The membranes showed the gross findings of two chorionic membranes each with its amniotic membrane showing slight maceration.

Diagnosis.—Double ovum twin placentas, fused, one battledore with ischemic necrosis (white), avascular, with maceration and meconium staining; one slight premature placenta; placenta from twins; one macerated stillborn, and one living infant.

SUMMARY

A primipara, aged 34 years, with a twin pregnancy, developed signs of toxemia in the twenty-eighth week. The toxemia suddenly abated at the end of the thirty-sixth week. Two weeks before term she was delivered of dizygotic twins, the first a living female, and the second a macerated male. The latter's intrauterine death was estimated as coinciding with the clinical recession of the toxemia. The placentas were fused and the cords were inserted marginally at opposite ends. The smaller placenta showed areas of ischemic necrosis.

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UNILATERAL TWIN ECTOPIC PREGNANCY

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BETWEEN 1891, when De Ott[1] reported the first authentic case of unilateral twin ectopic pregnancy and August, 1939, when Kaplan[2] published two more case reports, a total of 67 instances have been presented in the world's literature. The interval papers of Arey[3] in 1923 and Falk and Blinick[4] in 1938 have been extremely effective in reviewing the recorded cases, bringing the totals to 40 and then 65. One other study has since been presented since Kaplan's paper, Recek reporting a case in May, 1939.[5] The following study is the only case that has occurred in the five-year existence of the Queens General Hospital, during which time there have been 4,222 gynecologic admissions, 7,530 obstetric deliveries, and 54 ectopic gestations, all the latter proved at operation.

Mrs. H. B. (No. A836) was admitted to the Second Gynecological and Obstetrical Service of the Queens General Hospital on Sept. 30, 1939, complaining of eight hours of severe abdominal pain. The patient was a 25-year-old white housewife, whose medical and surgical past were entirely negative. Two previous pregnancies terminated in 1930 and 1932 in normal spontaneous deliveries at term. In 1935, the patient had a spontaneous abortion. None of these pregnancies were followed by a febrile course or any abdominal complication. Her last menstrual period began on July 15, 1939, and was normal in every respect.

Ten days before admission, on September 20, vaginal spotting was noted for the first time, lasting one day and subsiding spontaneously. Again on September 25 this slight spotting was seen by the patient, this time associated with lower abdominal cramps lasting two days and then disappearing spontaneously. During neither of these two episodes did the patient seek medical attention. On the day of admission there was a sudden recurrence of the pain, similar in character, localized to the right lower abdominal quadrant, far more severe than previously noted, associated with an initial attack of emesis and followed by intense perspiration and chills. In the eight-hour interval before admission to the hospital, there was no episode of fainting or shoulder pain.

When admitted to the hospital, the patient was acutely distressed. The blood pressure was 110 mm. of mercury systolic and 76 diastolic, pulse 100 per minute, and the temperature 99.4° F. The lungs and heart presented no pathologic findings. The abdomen was distended, diffusely tender, and showed marked rebound tenderness in both lower quadrants. The lower abdominal areas were spastic to deep palpation; no masses could be outlined. On vaginal examination it was found that the cervix was in the axis of the vagina, soft, and extremely tender on motion. The uterine fundus was anterior and, although not clearly defined, gave the impression of being slightly enlarged. In the left fornix, a soft, tender mass about 4 or 5 cm. in diameter was palpated. No bulging could be found in the posterior cul-de-sac. The urine was normal. Blood examination revealed a white cell count of 11,800 with 84 per cent polymorphonuclear cells, a red cell count of 3.5 million cells, and a hemoglobin of 11 Gm. (Sahli). The Kline test was negative.

Diagnosis was ruptured ectopic pregnancy, and the patient was immediately prepared for operation. Under cyclopropane anesthesia, the abdominal cavity was opened with the release of large amounts of clotted and fluid blood. The uterus was softened and enlarged to the size of a two months' pregnancy. Both ovaries and the right tube were normal. The left tube was dilated at the junction of the middle and outer thirds, the dilatation presenting a distinct area of rupture with a slow, constant ooze of blood. A left salpingectomy was performed, including the excision of the cornual end of the tube. The patient's postoperative course was uneventful, and she was discharged on her eleventh convalescent day in excellent condition.

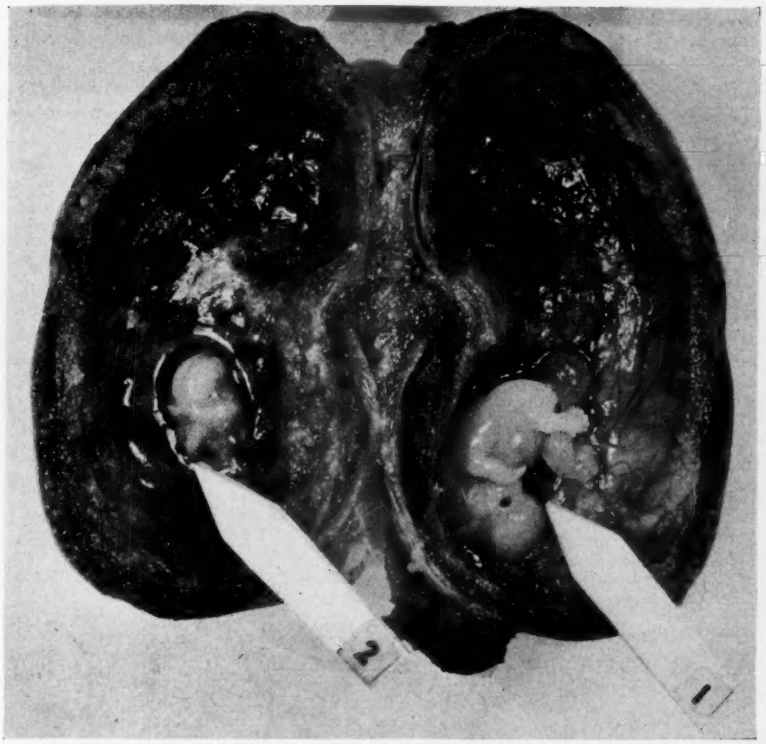

Fig. 1.—Dilated portion of tube divided to show the single chorionic sac surrounding the two fetuses.

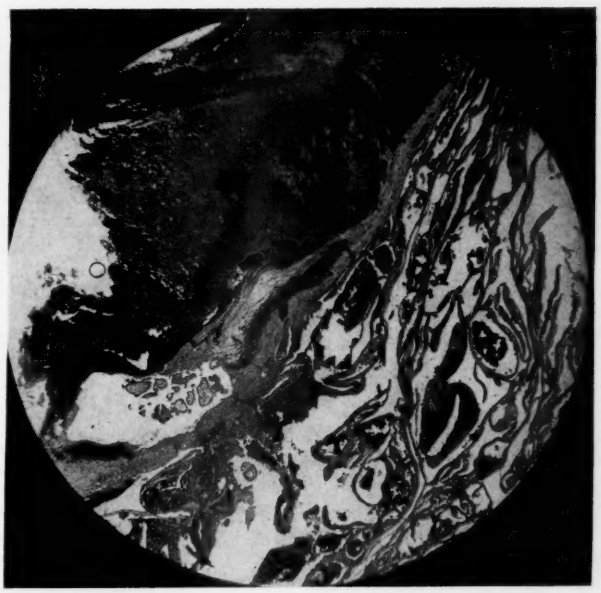

Fig. 2.—Section of the wall of dilated tube showing flattened epithelial folds, chorionic villi, and blood clot.

The pathologist's report of the tubal pregnancy was as follows:

"Gross.—The specimen (Fig. 1) consists of a cystic tubular mass measuring 8 by 3 cm. The external surface is smooth with a surface dullness. On cut section, the cystic content is found to consist of a clear fluid. A single large sac measures 6 cm. in length and 2½ cm. in width. The inner amniotic lining is glistening and shows dilated, thin-walled superficial vessels radiating toward the umbilical cord which is well formed in one fetus. This well-formed fetus measures 2 cm. in length and has an attached yolk sac measuring ½ cm. in diameter that is easily recognizable. The umbilical cord is short and shows some coils. The limb buds are easily distinguished. The other fetus is somewhat smaller in size and the presenting length measures only 1½ cm. The limbs are not as differentiated. The wall of the mass shows thickening, hemorrhage and suggests an encircling chorion.

"Microscopic.—The section of the tube (Fig. 2) shows the hypertrophic muscular layer and the hyperplastic mucosa. In addition, the mucosa shows a decidual reaction with a large attached blood clot in which numerous chorionic villi are present.

"Diagnosis.—Twin tubal pregnancy, monochorial."

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DIPHTHERITIC VAGINITIS IN THE ADULT

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THE Klebs-Loeffler bacillus grows best on an alkaline medium and in an abundance of air. It is rarely found in the vaginal flora. Since most women have some degree of immunity to diphtheria, it is quite uncommon for true diphtheritic vaginitis to occur in the adult.

In the following case, the predominating vaginal infection was a primary diphtheria with spontaneous expulsion of a complete cast of the vagina followed by vaginal atresia.

CASE REPORT

J. H., aged 22 years, colored, gravida iii, was admitted to Gallinger Municipal Hospital on Oct. 19, 1939, complaining of a painful sore on her perineum. She had had a slightly sore throat, fever, and a headache for a week. On Oct. 15, 1939, the patient became aware of a nodular swelling of the right labium majus and of an ulcer of the perineum with associated severe and persistent pain. The patient's mother had been treating the ulcer with a cresol antiseptic solution. Menstrual periods had been regular. Last period began on Oct. 11, 1939, and was completed the day before admission. Patient had given birth to two full-term infants. Last pregnancy terminated spontaneously in the fifth week in 1935. She had been married twice. Past medical history included whooping cough, measles, and mumps. In 1936, the patient was treated for gonorrhea.

Physical Examination.—Patient was a well-developed, fairly well-nourished, acutely ill, colored woman, restless and in severe pain. Temperature, 103.2° F.; pulse, 122; respirations, 24; and blood pressure, 110/52. Skin was hot and dry. Gums receded. Tongue was coated. Pharynx showed slightly reddened areas around the faucial ring, but no ulceration or membrane. Chest, breasts, and heart were normal. Abdomen was flat and soft with generalized tenderness to palpation. External genitals were edematous. A tender, fairly firm, right Bartholin gland, 6 cm. in diameter, was present. A ragged, granular, reddened ulcer, 3 cm. by 4 cm. in-

volved the fourchette. Foul, yellowish brown, watery discharge was coming from the vagina. As much of the vaginal mucosa as could be exposed appeared gangrenous.

Laboratory Findings.—Repeated smears and culture were negative for gonococci. Dark-field examination was misleading in that spirochetal organisms were found, but they were not identified as the *Treponema pallidum*. Kahn tests were negative on Oct. 19, 1939, Nov. 27, 1939, and Jan. 24, 1940. Urinalyses were normal except for one-plus albumin. Blood count varied from Hb. 70 per cent; red blood count 3,000,000, white blood count 14,700, on admission to a low of Hb. 33.4 per cent, red count 2,600,000, and white count 7,000, on Nov. 24, 1939.

Progress.—Preliminary diagnoses were confusing. Acute Bartholinitis was obvious, but gonococci were absent in smears and culture. The ulcerative lesion suggested secondary syphilis, but the Kahn test was negative. Etiology of the gangrenous vaginitis remained obscure until Oct. 26, 1939, when the patient passed a hollow cast of the vagina 10 cm. by 7½ cm. by 1 cm. External surface of the cast was dirty, grayish brown, and moderately trabeculated throughout. Inner surface was granular, covered by a light brown cheesy material. Cut surface showed a homogenous gray tissue. Microscopic examination of the cast showed a mass of necrotic tissue. McCallum stain showed the presence of diphtheria bacilli in the necrotic tissue. Following passage of the cast, the vagina showed rough, granular, extremely tender areas of ulceration.

The cast suggested diphtheritic vaginitis. Vaginal and nose and throat cultures were taken immediately. Three nose and throat cultures were negative for diphtheria. Two vaginal cultures were morphologically positive for diphtheria. Virulence tests were positive. On Nov. 3, 1939, the patient's five-year-old daughter was admitted to the Isolation Ward with faucial diphtheria. The child had had a sore throat for four days.

Before discovery of diphtheria, the patient had been given sulfanilamide and a blood transfusion. Fever was irregular ranging from 98 to 104° F. Following the injection of 20,000 units of diphtheria antitoxin and a second blood transfusion, clinical improvement was rapid. By Nov. 17, 1939, the ulcer of the fourchette had healed completely, the right Bartholin gland was soft, fluctuant, and non-sensitive. Fibrinous adhesions between the cervix and vagina obliterated the vaginal vault. Under evipal anesthesia, the thin vaginal adhesions were dissected digitally and the vagina was packed tightly with vaseline gauze. Packing was removed on the fifth postoperative day. At the time of discharge from the hospital, Dec. 7, 1939, three negative vaginal cultures for diphtheria had been obtained. The vagina was showing some generalized constriction. One week later, there was an annular constriction just inside the hymenal ring which reduced the orifice to a diameter of about 2 cm. Dense adhesions had formed around the cervix.

During the year that the patient has been under observation, constricting bands have been excised from the vagina twice. The right Bartholin gland has been removed. Culture of its contents was negative for diphtheria. For the first five months after leaving the hospital, the patient wore a pyrex vaginal plug constantly. Severe postinflammatory scarring of the vault has reduced the depth of the vagina to about 5 cm. However, the vaginal orifice admits three fingers. The cervical os has remained open. The patient has had no dyspareunia, and menstrual function has remained normal.

This case demonstrates the value of accurate laboratory data in the differential diagnosis of ulcerative vulvovaginal lesions, confirms the importance of specific therapy in genital diphtheria, and presents a problem in acquired vaginal atresia.

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Society Transactions

CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

TWELFTH ANNUAL MEETING, INDIANAPOLIS, IND., OCTOBER 10 TO 12, 1940

The following papers were presented:

Presidential Address: Continuation Study. Dr. Jennings C. Litzenberg, Minneapolis, Minn. (For original article, see page 547.)

Local Anesthesia in the Second and Third Stages of Labor. Dr. Roy E. Crowder, Sioux City, Ia.

The Relative Effect of Analgesia and Anesthesia in the Production of Asphyxia Neonatorum. Drs. Harold Henderson, E. Bruce Foster, and L. S. Eno, Detroit, Mich. (For original article, see page 596.)

Solid Teratoma of the Ovary in the Young Girl. Dr. Merrill Smeltzer, Detroit, Mich. (For original article, see page 616.)

Dental Caries in Pregnancy. Dr. Joseph D. James, Springfield, Mo.

A Study of One Hundred and Seven Cases of Uterine Bleeding With Endometrial Biopsies. Dr. Gilbert F. Douglas, Birmingham, Ala. (For original article, see page 624.)

The Leucocyte Count in Labor. Dr. John R. Wolff (by invitation), Chicago, Ill. (For original article, see page 611.)

The Differential Diagnosis of Acute Appendicitis in the Female. Dr. H. E. Schmitz, Chicago, Ill.

The Vaginal Smear (Papanicolaou) Prior to the Menopause in Menstrual and Reproductive Disorders. Dr. P. F. Schneider, Evanston, Ill.

The Economic Status of Obstetrical Care in North Dakota. Dr. P. W. Freise, Bismarck, N. D.

Inhibition of Lactation. Drs. H. L. Stewart, Jr. (by invitation) and J. P. Pratt, Detroit, Mich. (For original article, see page 555.)

Some Aspects of the Pathology of Hydatidiform Mole and Chorionepithelioma. Dr. Robert Meyer, Minneapolis, Minn.

Blood Prothrombin Levels in the Newborn. Drs. Carl P. Huber and Jack C. Shrader (by invitation), Indianapolis, Ind. (For original article, see page 566.)

Breech Delivery. Dr. Elmer M. Hansen, Lincoln, Neb. (For original article, see page 575.)

The Therapeutic Value of Tubal Patency Tests in Sterility and Infertility. Drs. M. L. Leventhal and E. M. Solomon (by invitation), Chicago, Ill. (For original article, see page 628.)

Conglutinatio Orificii Externi as a Factor in Delayed Labor. Dr. Philips J. Carter, New Orleans, La. (For original article, see page 606.)

Pituitary Extract for Dystocia Due to Uterine Inertia in the First Stage of Labor. Drs. R. S. Siddall and D. G. Harrel (by invitation), Detroit, Mich. (For original article, see page 589.)

Are the Anterior Pituitary-Like Substances Gonadotropic? Drs. Willis E. Brown, Omaha, Neb., James T. Bradbury, Ann Arbor, Mich., and Ida Metzger, Ypsilanti, Mich. (For original article, see page 582.)

NEW YORK OBSTETRICAL SOCIETY

MEETING OF NOVEMBER 12, 1940

The following case reports and papers were presented:

Report of a Case of Submucous Fibroid or Sarcoma Removed Vaginally During Labor. Dr. Richard N. Pierson.

Report of a Case of Lateral Pyocolpos With Absence of One Kidney. Dr. Max D. Mayer, and S. H. Geist.

Postpartum Sterilization. Dr. Fred L. Adair. (By invitation.)

CHICAGO GYNECOLOGICAL SOCIETY

MEETING OF NOVEMBER 15, 1940

The following papers were presented:

The Place of Surgery in Fibroids of the Uterus. Dr. C. W. Barrett.

The Occurrence of Diphtheria Antitoxin in the Human Pregnant Mother, Newborn Infant and the Placenta. Drs. J. Liebling, G. P. Youmans and H. E. Schmitz. (For original article, see page 641.)

Pituitrin Shock. Drs. M. H. Adelman and B. B. Lennon. (For original article, see page 652.)

Lissimore and Currie: Studies in Vaginal Fluid, J. Obst. & Gynaec. Brit. Emp. **46:** 673, 1939.

A series of 105 cases of vaginal discharge was examined. The majority of patients (66.9 per cent) were the hosts of *Trichomonas vaginalis.* This organism in the opinion of the authors is not pyogenic but is associated with a lowering of the normally high acidity of the vaginal contents, and thus with removal of one of the most powerful barriers to infection by pyogenic invaders, of which the *Staphylococcus pyogenes aureus* is by far the commonest in their series. This accounts for the frequent association of the flagellate with pus, secondary infection being more usually present. There are two possible explanations of this association of the flagellate with decreased activity:

A. The trichomonas is antagonistic to the bacillus of Döderlein. It also impedes the normal desquamation of vaginal epithelium. Thus both factors, closely associated with normal vaginal acidity, are reduced or absent.

B. The acidity of the vagina suffers great antecedent reduction by at least two natural factors, namely (1) the presence of menstrual lochia during periods, and (2) the deposition of semen during intercourse. The trichomonas, finding once again a medium of a pH agreeable to its existence, readily reestablishes itself. It is thus not necessary to postulate direct infection from the male during intercourse. Either of these two factors would explain the reappearance of trichomonas after apparent cure.

In the 33.1 per cent of cases in which trichomonas is absent, pyogenic infection explains the qualitative abnormalities of the vaginal fluid, and, as in the trichomonas positive cases, the *Staphylococcus pyogenes aureus* appears to be the commonest invader.

J. P. GREENHILL.

Correspondence

Relation of the Pituitary to the Etiology of Eclampsia

To the Editor.—

Dr. Geiling's collective review of the pharmacology of the pituitary in the November, 1940, issue of this JOURNAL admirably epitomizes present knowledge. There are, however, certain statements concerning "hypersecretion of the posterior lobe of the pituitary" related to the cause of eclampsia, which call for qualification and elaboration.

Basing my arguments on clinical observations and biologic experiments, I postulated the heightened activity of postpituitary principles in the pregnant organism sensitized by split-products of proteins, as derivatives of disintegrated syncytial elements, as a basic factor in the pathogenesis of pre-eclampsia and eclampsia. (Zentralbl. f. Gynäk., January, 1918.) As a corollary, I suggested the administration of corpus luteum preparations as a suitable method of therapeutically counteracting the hyperactive pituitary hormones (Zentralbl. f. Gynäk., 1920). To the usefulness of such treatment, proper emphasis was given on the basis of more extended investigations in later years, by Corner, Robson, McIlroy (Edinb. M. J., 1937; Tr. ed. Ob. Soc., p. 61), while Robson and Paterson, Young suggested that progesterone deficiency may be actively concerned in the pathogenesis of eclampsia (Brit. M. J. **1**: 1937).

The effects on vital organs of overdosage of pituitary pressor principles, as giving some indication of a hyperfunction of the gland itself, were studied with unflagging interest and energy. Designed to test our concept, Knepper obtained evidence of the occurrence in dogs, as the result of parenteral injections of proteins and subsequent exhibition of pitressin, of lesions in the parenchyma of the liver, the lung, brain, and kidneys, closely resembling changes known to occur in eclamptics (Zentralbl. f. Gynäk., 1934). Dodds and Noble demonstrated the production of gastric and intestinal ulcers in rabbits (Nature **135**: 788, 1935). Again, Byrom gave a critical digest of the experimental literature and demonstrated in the kidneys of rats which had received injections of vasopressin, lesions which were highly suggestive of those found in late toxemia of pregnancy. Of considerable interest were his additional studies showing that both, gonadotropic hormones and estrin, sensitize the blood vessels to vasopressin (Lancet **1**: 129, 1939).

In support of my assertion, I subsequently endeavored to adduce telling arguments by pointing to a remarkable parallel between well-known characteristics of the blood chemistry in eclamptics and the findings in the blood of animals which had received intravenous administrations of posterior pituitary extract, notably the phenomenon of anoxemia of the tissues (AM. J. OBST. & GYNEC. **26**: 311, 1933). There was also stressed the marked response of the arterioles of the kidney to pitressin (Richards) by way of constriction.

Efforts to obtain direct evidence for the integral endocrine factor, by establishing an excess of pitressin in the blood of pre-eclamptics, invited acrimonious debate, with denials of such findings far in preponderance (Theobald, Byrom and Wilson, Wesselow and Griffith, Hurwitz and Bullock). In like manner, the histologic basis of functional postpituitary hyperactivity conditioned by stimulation through the invasion of basophilic elements (H. Cushing) was unable to withstand criticism. Quite recently, however, the subject entered a new phase. The concept that *natural secretion* of pitressin may reach toxic levels and may induce intense vascular spasm, in consequence of a specific sensitization of the arteriolar tree and the abeyance of antipressor principles, becomes proportionately more acceptable. As to the former, the augmented thyroid activity during pregnancy with increased quantities in the blood of thyroxine and iodine (G. Curtis) deserves to be placed

first on record (Clark). Certain split products of proteins, particularly histamine-like substances (Paulsson, Carleton), the above-mentioned sex hormones, hyperplasia of the adrenal cortex and the concomitant alteration of the salt balance, represent significant factors which may conduce to a heightened responsiveness of the arterioles to vasopressin. In normal pregnancy, an inhibitory factor which holds the effect of such stimuli in check was to be searched for. The key to the acute problem seems to be provided by consideration of the remarkable quantities of acetylcholine stored in the normal placenta.

Information bearing on a substance significantly constant, both as to presence and quantity in normal human placentas and pharmacologically identified as acetylcholine, had its inception in the investigations of Bischoff, Strack and Loeschke, Hauptstein, Chang and Gaddum (J. Physiol. **79**: 274, 1933). The release of acetylcholine into the maternal circulation is contingent on the unique position of the human placenta to maintain a broad and direct contact with the maternal intervillous blood spaces and continuously to shed from its surface syncytial buds with hormones and other chemical entities, stored or elaborated within the placenta. The recent experimental demonstration of an antagonistic pharmacodynamic action on the arteriolar tree of pitressin and the powerful vasodilator acetylcholine (Necheles and Neuwelt, Am. J. Physiol. **124**: 142, 1939) is of immediate interest and gives weight to the concept of the existence during normal gestation of a specific biochemical blood pressure regulating mechanism concerned with maintaining a well-defined equilibrium between pressure-raising principles and acetylcholine.

The assertion that pre-eclampsia virtually illustrates a dislocation of this equilibrium, with the arterioles hyperreactive to pitressin, will be found to diverge from obstetric orthodoxy which steadfastly clung to the idea that the placenta is the source of certain toxins. Presentation of the following facts, however, serves to bear out our contention. Determination of the acetylcholine content of placentas obtained from severe pre-eclamptics revealed quantitative data distinctly below the almost constant normal levels of 90 to 120 mg., calculated in terms per one kilogram of fresh organ. A preliminary report of this work was presented, in discussion, at the last meeting of the American Medical Association and an attempt made to correlate such *placental deficiency* with the well-known occurrence in the toxemic placenta, of multiple areas of infarction and autolysis. Spaeth, Eufinger and Sprado, of late, investigated the values for blood choline in normal and toxemic women and reported a marked decrease in 9 cases of pre-eclampsia studied. Eight out of 9 cases of eclampsia gave unusually low figures (Monatschr. f. Geburtsh. u. Gynäk. **101** and **102**: 1935, 1936).

Quite recently, through the kind cooperation of the department of pharmacology of Harvard Medical School, evidence was obtained concerning a most remarkable increase in placental tissue of the concentration of choline-esterase, in severe pre-eclampsia and eclampsia. Since the physiologic function of the enzyme concerns the removal of the acetylcholine liberated, strong support is obtained in favor of our conception.

The presumed function during gestation of placental acetylcholine as opposing the action of pitressin well accords with recent discoveries in animals of an inhibitor substance present in extracts of kidney and muscle. Significantly, decreased concentration of this substance renders animals unusually sensitive to the effects of renin (Page, Grollman, Tillman). The significance of reduced renal blood flow in the late toxemia of pregnancy, as the result of pitressin-induced angiospasm, is unequivocally portrayed in the experimental studies of Goldblatt.

J. Hofbauer, M.D.

Cincinnati, Ohio
Jan. 31, 1941.

Department of Reviews and Abstracts

CONDUCTED BY HUGO EHRENFEST, M.D.

Selected Abstracts

Malignant New Growths

Reidiger, K.: A Plan of Cancer Control in East Prussia, Deutsche med. Wchnschr. **66**: 155, 1940.

The author discusses the difficulties of discovering carcinoma in the examination of large groups of women. In 1,920 women examined, carcinoma of the breast was found in 7 cases, suspicious growths in 11. Carcinoma of the uterus was diagnosed in 4 cases, suspected in 36 others. Associated genital pathology was found in 645 cases. The technique of polariscopic examination of the blood serum for cancer, as developed by Brdička and Waldschmidt-Leitz, is fully described. Waldschmidt-Leitz claims to have a histologically proved accuracy of 95 per cent in over 500 cases of cancer diagnosed by this method. Reidiger favors the routine use of the colposcope.

R. J. WEISSMAN.

Filkel: Polarigraphic Study of Serum of Women With Carcinoma of the Genitalia, Zentralbl. f. Gynäk. **63**: 647, 1939.

A new serologic test for carcinoma is described by Filkel. In 176 cases of carcinoma, diagnosis was correctly made in 92.6 per cent, and among 107 cases of recurrence of cancer, the incidence of correct diagnosis was 88.9 per cent. Early carcinoma could be detected in 87 per cent of the cases. However, the cancer reaction is not specific, because a positive test may be obtained in cases of pelvic inflammation. Despite this, the test proved helpful in cases of recurrence and in doubtful cases.

J. P. GREENHILL.

Morse, A. H.: Problems and Errors in the Diagnosis of Cancer of the Uterus, Connecticut State M. J. **4**: 461, 1940.

One would assume that the recurrence of bleeding, subsequent to a complete freedom from discharge over an interval of months or years, would prove of significance to the patient or to her relatives, but too frequently the symptom is disregarded.

If ever we are to see the early stages of cervical malignancy, we must cease relying upon what are designated as the first signs of cancer, but must emphasize the necessity of a routine yearly, or better semi-annual, examination of the pelvic organs, even though no symptoms are present, for women in the menopause.

From a survey of a group of histories, however, it is clear that there are some members of the profession who wholly disregard the possible significance of abnormal uterine bleeding or who fail to suspect malignancy even when it is present. In 10 patients whose histories were reviewed, vaginal bleeding, in some instances profuse, was the sole cause of the visit to the physician. However, it appears that no pelvic examination was made in any of these cases. Some women were given a drug by mouth or vaginal douches were prescribed. Others were told that the bleeding was of no significance.

If the general practitioner can be brought to realize that the presence of abnormal discharge or bleeding from the vagina makes a pelvic examination imperative, it will be a great step forward.

J. P. GREENHILL.

Peller, Sigismund: Cancer and Its Relations to Pregnancy, to Delivery, and to Marital and Social Status, Surg., Gynec., & Obst. **71**: 1, 1940.

The distribution of primary neoplasms within the breast and genital organs, and the age-specific death rates from cancer of each part are widely influenced by birth rates; the total mortality from cancer of the breast and genital organs, however, varies only to a small degree, as an increase in incidence in one organ is compensated for by a decrease in incidence in other organs. The compensation is not an exact one, for populations with higher birth rates have a rather diminished mortality. These findings are corroborated by the clinical studies of the author (1922 to 1923).

From the standpoint of social status the changes in the incidence of uterine cancer and breast cancer become apparent. These changes are independent of those due to purely biologic relations, that is fertility and cancer rate.

In contradistinction to the factors considered, circumstances attendant upon the husband's death are likely to increase the mortality from both uterine and breast cancer, and so to change the age-specific frequency of cancer affecting both organs.

The lower the social level and the less satisfactory the marital status, the earlier the patient manifests cancer or dies from it.

The correlation between cancer and pregnancies in women is entirely different from that in mice.

WILLIAM C. HENSKE.

Peller, Sigismund: Cancer and Its Relations to Pregnancy and Delivery to Marital and Social Status, Surg., Gynec., & Obst. **71**: 181, 1940.

The total cancer mortality as well as the site of the primary tumor (genital organs, breast, stomach, biliary system, pancreas, and colon) is influenced by the marital status. During the age of reproduction married women show higher cancer rates than do spinsters; in the twenty years following, there are small differences in favor of married women; above the age of 64 both groups have about equal cancer mortality rates. These cases differ from one another only in the distribution of the primary tumors. In widows the age specific mortality rates are higher for cancer of genital organs, breast, stomach, pancreas, and colon than in single or married women; widows also succumb more frequently to gall bladder cancer than do single women.

There is a correlation between reproductive activity and the changes in the cancer distribution within the genital organs, the breast, biliary system, and stomach, the incidence increasing in some organs and in others diminishing. These changes counterbalance each other.

The simultaneous occurrence of cancer with pregnancy seems less frequent than would be expected, the deficit increasing as age advances, and as the average number of pregnancies increases.

WILLIAM C. HENSKE.

Leissner, H.: Myoma and Carcinoma of the Body of the Uterus, Acta. obst. & gynec. Scandinav. **20**: 106, 1940.

The author noticed a high frequency of the association of myomas with carcinoma of the uterine body, and reviewing the literature found this to be a fairly common observation. He points out that there is a far greater association of corpus carcinoma with myoma than of cervix carcinoma with myoma. He believes that myomas may play a part in the development of cancer of the endometrium, and that hyperplasia of the endometrium is an intermediary stage in the development of cancer. He found that corpus cancer usually is located in places which are difficult to reach, such as the site of attachment of the myoma to the uterus and in hidden corners.

J. P. GREENHILL.

Hall, Norman D.: Carcinoma of the Cervix in the First Three Decades of Life, Canad. M. A. J. **43**: 362, 1940.

Of 134 cases of uterine carcinoma occurring in persons under 30 years of age 57 represented carcinoma of the cervix. This is 7.4 per cent of all proved cervical carcinomas seen at the institution. There has been a proportionate increase in the frequency of cervical carcinoma in women 30 years of age or under during the past five years as compared with the previous five years. At least 37 per cent of this group were married before the age of 20 and 37 per cent had had one or more pregnancies before 20 years of age. The youngest patient seen was 20 years old. Abnormal bleeding was the first symptom in 95 per cent of the patient and was the only symptom in 50 per cent of the group. Of this group, 49 per cent died within two years after the diagnosis was made, and only 11.5 per cent lived over two years.

CARL P. HUBER.

Diddle, A. W.: Carcinoma of the Cervix Before the Age of Twenty Years, Am. J. Cancer **34**: 207, 1940.

From July, 1926, to Dec. 1, 1939, 505 cases of carcinoma of the cervix were diagnosed in the University Hospitals (Iowa). Five of the patients were less than 25 years of age; one was 17 years, two 21, one 23, and one 24. The available literature reveals 18 reports of cervical malignancy occurring before the age of 20. Only three of the tumors were designated as epitheliomas, while 9 were adenocarcinomas, and in six the type is not indicated. Of the 18 patients, 6 died within one year.

The impression is obtained that the prognosis of carcinoma of the cervix before the age of 20 is grave because of the accelerated growth impulse in malignant neoplasms during the growing years. The case reported by the author demonstrates the rapidity with which the neoplasm may invade the surrounding pelvic tissues, even during heavy irradiation therapy.

J. P. GREENHILL.

White, J. W.: Carcinoma of Uterine Cervix, Am. J. Surg. **45**: 4, 1939.

Microscopic examination of adequate biopsy material is the only means by which cancer of the cervix can be diagnosed with any degree of precision, and little hazard is involved in properly excising biopsy specimens. Colposcopic examination and the Schiller iodine test are of academic interest. Both are greatly subsidiary to unaided visualization and biopsy. The Schiller test is a purely negative diagnostic method. Palpation of the cervical broad ligaments is satisfactorily accomplished by a combined vaginorectal examination. The majority of cervical cancers are radiosensitive; and the more active and anaplastic the cells, the less their radioresistance. Cancer appearing in the cervical stump within one year after supravaginal hysterectomy is residual and was present before the operation. If it appears after a longer interval, it must be considered a subsequent primary new growth. As prophylaxis against the latter event the mucosa of the cervical stump including the endocervix, if not destroyed by cautery at the time of operation, must be so destroyed within four weeks thereafter. Radium irradiation efficiently administered is the safest and most certainly curative method of treatment, but it must be supplemented by high voltage roentgen rays in all except the earliest cases. Primary roentgen therapy, supplemented by postradium roentgen irradiation, offers advantages that require further evaluation. Radium is by no means a simple remedy that may be applied casually without disastrous effect or serious consequences. Therefore, it should be used only by those who have had an opportunity through supervised experience to become expert in its application. Although the absolute curability rate for cancer of the cervix is between 20 and 30 per cent, half the total number of patients treated will die of the disease within three years.

J. P. GREENHILL.

Annual Report on the Results of Radiotherapy in Cancer of the Uterine Cervix, League of Nations Health Organization 3: 1, 1939.

The definitions of the four stages of cancer of the cervix uteri accepted by the League of Nations are as follows:

Stage I. The carcinoma is strictly confined to the cervix.

Stage II. The carcinoma infiltrates the parametrium on one or both sides, but does not invade the pelvic wall. The carcinoma infiltrates the vagina, but does not involve its lower third. Endocervical carcinoma spreads to the corpus.

Stage III. The carcinomatous infiltration of the parametrium invades the pelvic wall on one or both sides. On rectal examination, no cancer-free space is found between the tumor and the pelvic wall. The carcinoma involves the lower third of the vagina. Isolated carcinomatous metastases are palpable on the pelvic wall (irrespective of the extent of the primary cervical growth).

Stage IV. The carcinoma involves the bladder as determined by cystoscopic examination or by the presence of a vesicovaginal fistula. The carcinoma involves the rectum. The carcinoma has spread outside the true pelvis (below the vaginal inlet, above the pelvic brim, distant metastases).

This annual report, the third of the series, includes statements from 16 radiotherapeutic centers.

The statements provided by these centers vary considerably with respect to the number of years to which they relate and to the number of patients treated yearly in each center. When all the data in them are combined, they furnish information concerning 9,061 patients suffering from cancer of the uterine cervix examined with a view to treatment, of whom 7,958 (87.8 per cent) were submitted to radiologic treatment.

The following tabular statement shows the results obtained after the lapse of five years from the date of treatment:

		PER CENT
Alive without recurrence	2,194	27.6
Alive with recurrence (including those operated upon after failure of radiotherapy)	128	1.6
Died of cancer	5,368	67.5
Died of intercurrent disease	163	2.0
Lost sight of	105	1.3
	7,958	100.0

The 7,958 patients treated were allocated to stages as follows:

		PER CENT
Stage I	871	10.9
Stage II	2,305	29.0
Stage III	3,420	43.0
Stage IV	1,360	17.1
Unclassified	2	0.03
	7,958	100.0

Results of treatment calculated for each of the four stages:

	NUMBER OF PATIENTS TREATED	ALIVE WITHOUT RECURRENCE	RELATIVE CURE RATE PER CENT
Stage I	871	498	57.2
Stage II	2,305	867	37.6
Stage III	3,420	754	22.0
Stage IV	1,360	75	5.5
Unclassified	2	0	0.0
Grand total	7,958	2,194	27.6

J. P. GREENHILL.

Warren, Shields, Meigs, Joe V., Severance, Alvin O., and Jaffe, Henry L.: The Significance of the Radiation Reaction in Carcinoma of the Cervix Uteri, Surg., Gynec., & Obst. **69**: 645, 1939.

The histologic grade of carcinoma of the cervix is of less importance in prognosis than the clinical classification.

The response to radiation of either tumor cells or stroma is a definite guide to radioresistant cases; practically all those failing to show radiation changes on the early biopsies die of their carcinoma in spite of intensive radiation therapy. It is believed that such cases should be treated surgically.

WILLIAM C. HENSKE.

Meigs, Joe V., and Jaffe, Henry L.: Carcinoma of the Cervix Treated by Roentgen-Ray and Radium, Surg., Gynec. & Obst. **69**: 257, 1939.

This paper deals with 70 patients who have been followed and studied very carefully. It shows that the results of the treatment of cancer of the cervix with x-ray and radium are eminently satisfactory. It is evident that certain charts of prognostic value can be made, and the curves induce the authors to believe that it is no longer necessary to follow patients for five years before reporting on them but that a three-year follow-up from the time of treatment should suffice. If, from the end-results at three years, 15 per cent is deducted for the next two years, the approximate five-year results can be predicted. Therefore, more opportunities are given to the gynecologist and radiologist to change a given form of treatment.

The routine study of microscopic slides, while the patient is being seen, is of great value. The presence or absence of a proper microscopic radiation reaction is an important prognostic sign. The authors advise that in every cancer clinic the slides be looked at at the same time that the patients are examined.

Biopsies should be taken before treatment starts and after treatment to determine whether or not radiation is satisfactory as determined by the radiation reaction.

In this series of cases it is evident that kidney lesions due to blocked ureters with subsequent uremia are among the chief causes of death. More urologic investigations should be undertaken and they should be made before, during, and following treatment. Any indication of ureteral block should be treated as early as possible.

Since using a slower type of treatment with x-ray and radium, the patients have been more comfortable and their convalescence, after leaving the hospital, has been much easier. This type of treatment delivers more effective radiation about and around the cervix than can be delivered by radium alone. Areas of tumor on either side of the cervix are certainly reduced in size and may be destroyed. The field of radiation in the broad ligaments and about the cervix before the radium is given is well walled-off by tissue reaction and fibrosis. Therefore, trauma of the cervix from curetting or application of radium will not cause extension of disease.

WILLIAM C. HENSKE.

Rosh, Rieva: Factors Influencing the Prognosis in the Treatment of Carcinoma of the Cervix, Radiology **35**: 17, 1940.

The therapy and complications arising from the treatment of carcinoma of the cervix by means of roentgen rays are reviewed. This review covers a total of 795 cases observed in the radiation therapy department of the Bellevue Hospital. The author feels that there is no absolute knowledge by which one can determine which type of carcinoma is resistant or sensitive to radiation, and therefore no attempt was made to group this series according to histologic study. In general the course of the therapy consisted of preliminary x-ray therapy to the pelvis, followed by radium administration to the cervix and uterus, and subsequent x-ray therapy to the pelvis four weeks later. Certain well-known complications to the skin, urinary tract, pelvic lymph nodes, rectum, and vagina are discussed. The poor results in cervical

stump cancer are due, according to the author, to an absence of the uterine body which may prevent the correct application of a sufficient dose of radium. Emphasis is again placed on the fact that an adequate dose of radium applied to the cervix is capable of controlling the disease only in and directly adjacent to the cervical tissues.

WILLIAM BERMAN.

Smith, George Van S., and Pemberton, Frank A.: Carcinoma of the Uterine Cervix, New England J. Med. 222: 481, 1940.

Of the 997 consecutive cases with a clinical diagnosis of cervical cancer, seen at the Free Hospital for Women clinic from May, 1876, to January, 1934, 69 had had their primary treatment elsewhere and 148 cannot now be proved to have had the disease. This paper discusses in detail from various angles the remaining 780 consecutive cases, previously untreated and pathologically confirmable, encountered from October, 1902, to January, 1934.

But a few of the several important conclusions drawn from a thorough analysis of this large series of cervical cancers, observed during a long period of time, can be quoted here. As previously stated by other authors, this study shows the necessity, as part of the follow-up regime, to include periodic investigation of the whole urinary tract. Clinical classification and pathologic grading prove practically valueless in the evaluation of therapy. Since improved results have been associated, first, with the use of radium and then with addition of supplementary x-radiation, the indications for surgery have become greatly restricted. The appreciable incidence of carcinoma in cervical stumps, also in nulligravidas, re-emphasizes the desirability of removal of the cervix with the uterus, if feasible. Retreatment for recurrence is salutary in but few instances. In this series, 67 per cent of those apparently free of disease at five years are found to be well at ten years after primary therapy. There were six unquestionable cases of multiple malignancy in this series.

HUGO EHRENFEST.

Auster, Lionel S., and Sala, Angelo M.: Causes of Death in Cancer of the Cervix Uteri, Surg., Gynec. & Obst. 71: 231, 1940.

Cancer of the cervix is amenable to successful treatment by radiation in various forms and combinations. The literature contains numerous authoritative and well-substantiated reports of five-year cures and over. Such results can be obtained only when adequate treatment is given to patients in the early stage of their disease, and then continuous follow-up observation and treatment maintained.

There has been no previous attempt to evaluate accurately the causes of failure in the therapy and the real cause of death of the greater number of even presumably well-treated patients.

Curative therapy is useless in clinical Stages 3 and 4 cases. Even though the local visible vaginal lesion may be banished and its recurrences controlled, most cases eventuate in necrosis with ulceration and severe local infection. The paramount difficulty in treatment is the control of the progressive damage to the urinary tract which is involved in almost all late cases. Superimposed infection results in an overwhelming majority of the cases and is the outstanding cause of death. Although infection of the urinary tract is the most important source of sepsis, peritonitis forms a large group which has not previously been sufficiently recognized since the process is frequently clinically silent.

Metastases of widespread character are not uncommon and should be noted more often in the future as therapeutic measures become more widespread in their application, resulting in longer life for these patients who, untreated, usually die within eighteen months. Bone metastases, both of hematogenous skeletal distribution and of direct contiguous pelvic type, will be noted as patients live long enough to develop them. Thoracic lesions are also to be noted.

The most striking feature of this study, aside from the pathologic findings, has been the realization that most patients come for treatment when they are already in an advanced stage and have had significant symptoms extending over from six to twelve months before seeking medical advice. With the remarkable progress that has been made in the techniques of therapy, the next step in the control of cervix cancer lies in the road of education, both lay and professional, to make both patients and physicians appreciate the possible significance of abnormal vaginal bleeding.

WILLIAM C. HENSKE.

Dörr, H.: Metastases in Genital Carcinoma of Women, Particularly Bone Metastases, Fortschr. a. d. Geb. d. Röntgenstrahlen **60:** 100, 1939.

Dörr states that American radiologists maintain the rarest site for metastases of cervical carcinoma to be the bones of the skeletal system. Within the past year, however, he observed 10 cases of skeletal metastases. He had previously reported 2 cases of spontaneous fracture from such metastases. The author does not know whether or not the French radiologists are correct in their assumption that the insertion of radium is responsible for the occurrence of bone metastases. He agrees with them that too large doses of radium should not be used in order to avoid local trauma. He is convinced that neither operation (abdominal or vaginal) nor roentgen ray therapy produces skeletal metastases. In spite of the bad prognosis of bone metastases, x-ray or radium therapy should be carried out in order to lessen the severe pain in the periosteum which is associated with these metastases.

J. P. GREENHILL.

Masson, James C., and Gregg, Robert O.: Carcinoma of the Body of the Uterus, Surg., Gynec. & Obst. **70:** 1083, 1940.

The histories of 907 patients suffering from malignant lesions of the body of the uterus seen at the Mayo Clinic from Jan. 1, 1910, to Dec. 31, 1933, inclusive, have been reviewed. Eight hundred eighty patients were treated and traced for five years or more. Seven hundred thirty-two patients were seen primarily at the clinic with definite carcinoma of the body of the uterus; 728 were treated. In 22 additional cases there was carcinoma of the body and cervix; in 18 more there was carcinoma of the body of the uterus and of the ovary, and in 1 there was carcinoma of the body of the uterus and a fibrosarcoma of the ovary. Forty-seven patients suffering from recurrent carcinoma after treatment elsewhere were seen at the clinic. Three cases of carcinoma and fibrosarcoma in the same specimen were found in the same period. Eighty-four patients suffering from sarcoma were seen in the same period, 82 of whom were traced for five years or more. An analysis of 732 cases of primary carcinoma of the fundus is presented in detail.

Two hundred twenty-one patients were premenopausal, 510 postmenopausal. The average age at menopause of the postmenopausal group was 50.27 years, that of a control group 49.9 years.

Metrorrhagia was complained of by 660 patients, or 90.2 per cent. Its average duration was eighteen months. An abnormal discharge was present in 502 patients, or 68.6 per cent. On the average it had persisted 16.4 months. Menorrhagia occurred in 119, or 56.1 per cent, of 212 premenopausal patients. It had lasted 49.6 months on the average. Pain occurred in 204 patients, or 27.9 per cent, persisting on the average for 13.2 months.

Leiomyomas of the uterus were associated with carcinoma of the fundus in 215 of 590 cases in which operation was performed, an incidence of 36.4 per cent.

Of 257 cases in which the histologic grade was determined, 57 were graded 1, 134 graded 2, 31 graded 3, and 35 graded 4.

In 467 cases which it was possible to classify as to stage of growth, there were 89 Stage 1, 217 Stage 2, 77 Stage 3, and 84 Stage 4.

Only 59.6 per cent of Grade 1 lesions were postmenopausal, whereas 82.9 per cent of Grade 4 lesions occurred in the postmenopausal group. There was no significant difference in different grades as to discharge, anemia, or pain.

The hospital mortality for all treated patients suffering from pure carcinoma of the fundus was 38, or 5.22 per cent. Fourteen deaths were due to peritonitis and 12 to pulmonary emboli.

The five-year survival of 711 traced patients suffering from distinct carcinoma of the fundus was 425 cases, or 59.8 per cent. The ten-year survival of 520 traced patients was 252, or 48.5 per cent. The five-year survival of all patients having carcinoma of the fundus including those with carcinoma of cervix and ovary was 56.9 per cent. Omitting the recurrent cases, the five-year salvage was 59.4 per cent. The five-year survival of 86 traced Stage 1 patients was 72, or 83.7 per cent; of 210 traced Stage 2 patients, 74.3 per cent; and of 76 traced Stage 3 patients, 60.5 per cent; and of 49 traced Stage 4 patients on whom operation was performed, 24.5 per cent. The five-year survival of 57 Grade 1 traced patients was 77.2 per cent; of 134 Grade 2 patients, 64.9 per cent; of 31 Grade 3 patients, 61.3 per cent; and of 31 Grade 4 patients, 41.9 per cent. Six of 22 patients with carcinoma of the body and also of the cervix lived five years after treatment. Of 47 patients with recurrent pelvic carcinoma, probably arising in the body of the uterus, 8 were living five years after treatment.

Forty-two patients whose lesions were technically operable but who were irradiated alone because of their poor general condition gave a five-year salvage of 25, or 59.5 per cent, whereas the five-year survival of all patients with Stage 1, 2, or 3 growths on whom operation was performed was 73.1 per cent. The average age of the irradiated group, however, was 63.4 years, whereas the average age of the group operated upon was 55.5 years.

The occurrence of leiomyoma with carcinoma had little influence on the symptoms or prognosis in fundal carcinoma. Anemia was the single factor more common in patients with leiomyoma than in the rest of the group.

Eighty-four patients with sarcoma of the uterus were primarily treated at the Mayo Clinic in this period. Eighty-two of this group were traced five years. Of them 45, or 54.9 per cent, were living at the end of this period. The hospital mortality was 2 cases, or 2.4 per cent.

In 3 cases there were both sarcoma and carcinoma in the same specimen. Each case was in the Stage 2 classification, and each patient lived more than five years.

WILLIAM C. HENSKE.

Gunning, R. E. Lee, and Ross, Charles: Rhabdomyosarcoma of the Corpus Uteri, Surg., Gynec. & Obst. **70**: 230, 1940.

Rhabdomyosarcoma signifies a tumor containing striated muscle cells of embryonic type. Rhabdomyosarcoma of the corpus uteri is very rare, only 10 cases having been reported to date. A new case, occurring in a 58-year-old woman ten years past the menopause, is described clinically and pathologically. A summary of all cases so far reported reveals the fact that these tumors occur in women past the menopause, that they are prone to metastasize, and that all contain embryonic forms of striated muscle cells.

WILLIAM C. HENSKE.

Meigs, Joe Vincent: Cancer of the Ovary, Surg., Gynec. & Obst. **71**: 44, 1940.

Cancer of the ovary of the solid type is a very serious neoplasm.

Cancer of the ovary of the malignant papillary cystadenoma type is about as malignant as any other epithelial growth.

Early diagnosis and methods for early diagnosis are necessary to improve the end-results. The use of the peritoneoscope should prove of extreme value.

Bilateral oophorectomy with total hysterectomy is the proper treatment. Involvement of the uterus, adhesions, and growth through the wall of a tumor are extremely dangerous.

The rupture of cysts before and during operation is condemned, but the results of this series cannot support the condemnation. It is the author's belief that spilling of cyst contents should be avoided.

X-ray treatment to date has not proved of much curative value but more modern methods may.

Every cystic or solid tumor of the ovary that is removed should be opened by the surgeon before the wound in the abdomen is closed.

If cancer is found in a single ovary by the pathologic department, resort should not be made to radiation but the patient should be re-operated upon and radical surgery carried out.

WILLIAM C. HENSKE.

Maizels, Gerald: Probable Chorionepithelioma in a Virgin of Seventy-One, Lancet **1**: 690, 1940.

The author describes an abdominal tumor removed at autopsy from a 71-year-old virgin. The menopause had occurred twenty years previously, and no bleeding had been present until three months before death. Examination under anesthesia two weeks before death revealed an intact hymen with the vulva, cervix, and vagina consistent with virginity. A mass connected with the uterus reached halfway to the umbilicus.

The tumor proved to be a typical and highly malignant chorionepithelioma. Metastases were present in the lungs and liver.

The author suggests as the most reasonable explanation that the tumor originated from a teratoma of the uterus. Unfortunately the ovaries were not examined microscopically but both were grossly normal.

CARL P. HUBER.

Brown, Snodgrass, and Pratt: Latent Choriocarcinoma, Am. J. Cancer **38**: 564, 1940.

Latency, the concealed retention of potentially or actually malignant cells in a dormant state over a long period of time, is a curious and important phenomenon which has been observed in numerous types of malignant tumors. Because of the foreign nature of the cells of the placental chorion, and the presumably easy establishment of the date of their origin, latent chorionepithelioma has attracted particular attention. Several series of such cases have been collected, showing occasionally a latency of over five years—in one instance a period of thirty years having passed between the last pregnancy and discovery of the tumor at the age of seventy.

To the small group of cases in which proof of latency is apparently conclusive, another is added, in this paper.

This patient was curetted in 1927 for a hydatiform mole. Two years later a total hysterectomy was done for continued severe uterine hemorrhages. No evidence of a new growth could be found in the specimen. She seemed perfectly well for next six years when (32 years old) she was admitted to the hospital for persistent productive cough, with hemoptysis for five months. An exploratory thoracotomy revealed a large mass in the upper half of the right lower lobe. Patient died eight weeks later. Autopsy showed typical choriocarcinoma through both lungs. No evidence of the tumor was found in the pelvis or in any of the pelvic or abdominal lymph nodes.

It seems clear from both clinical and pathologic findings that the final development of the tumor began in the right lung. The original source of the chorionic tissue seems undoubtedly to have been the vesicular mole, which represented the patient's last known pregnancy.

It might be assumed and seems most plausible that simple pulmonary embolism of benign molar tissue occurred during the original curettement, with malignant change taking place only years later.

HUGO EHRENFEST.

Brewer, John I.: Kraurosis and Leucoplakia of the Vulva, Illinois M. J. **77:** 26, 1940.

Kraurosis vulvae is a condition of the skin most frequently seen in the region of the clitoris, labia minora, perineum, and labia majora. The lesion is white and the tissues appear shrunken but in some instances edema may produce a thickened skin. Fissures and ulcerations are frequently encountered. The author denies the statement that all atrophic lesions of the vulva with shrinkage as observed grossly are to be classified as kraurosis vulvae and uses senile atrophy as an example to prove his case. He also differs with Taussig, stating that it is not necessary for hypertrophic epithelial changes to precede the kraurosis.

Leucoplakia is described as a gray, blue, gray white, or white lesion of the vulva. The skin appears thickened. Fissures and ulcerations occur.

Leucoplakia and/or kraurosis are seen in association with all cancers of the vulva and because of this fact treatment should consist of a complete vulvectomy. Other forms of treatment such as endocrine therapy, nerve resection, hydrochloric acid, and vitamin A therapy may bring about temporary improvement only, and it seems unwise to use these measures in lesions which are so frequently associated with cancer.

EUGENE S. AUER.

Sparrow, Thomas D.: Leukoplakic Vulvitis, Ann. Surg. **112:** 87, 1940.

The author reviews the literature of leucoplakic vulvitis, and refers to the various names which have been given to somewhat related conditions, such as, kraurosis vulva and atrophic vulvitis. He reports 6 cases of his own. After all of the confusion is cleared up concerning the etiology of this condition, the most important factor seems to lie in ovarian dysfunction, or cessation of hormonal activity. He feels that there are probably other factors which as yet are unknown to us. Normally ovarian hormone exerts some protective influence over the genital skin, and in certain women withdrawal of the hormone results in an inflammatory process with leucoplakia and kraurosis as its principal gross manifestations. The pathologic processes from the primary swelling and hypertrophic changes to the atrophic stages are reviewed.

He points out that treatment with vitamin A, hydrochloric acid, and hormones have proved unsuccessful, and he feels that surgery is the best choice of treatment. It relieves the distressing symptoms and eradicates a definitely precancerous condition. Surgery was used in all 6 cases reported, with malignancy in 1 case. Postoperative complications occurred in all but 1 case. These consisted chiefly in a recurrence of subjective symptoms. Four of these patients were treated with estrogenic ointment (Foss) with some relief of the symptoms.

WILLIAM BERMAN.

Items

American Board of Obstetrics and Gynecology

The general oral and pathological examinations (Part II) for all candidates (Groups A and B) will be conducted at Cleveland, Ohio, by the entire Board from Wednesday, May 28, to Monday, June 2, 1941, inclusive, prior to the opening of the annual meeting of the American Medical Association in Cleveland.

Formal notice of the time and place of these examinations will be sent each candidate several weeks in advance of the examination dates.

Candidates for *reexamination* in Part II must make written application to the Secretary's Office before April 15, 1941.

The Board requests that all prospective candidates who plan to submit applications in the near future request and use the new application form which has this year been inaugurated by the Board. The Secretary will be glad to furnish these forms upon request, together with information regarding Board requirements. Address Dr. Paul Titus, Secretary, 1015 Highland Building, Pittsburgh (6), Pennsylvania.

"The Foundation Prize" of the American Association of Obstetricians, Gynecologists and Abdominal Surgeons

Rules Governing the Award

(1) "The award which shall be known as 'The Foundation Prize' shall consist of $150.00.

(2) "Eligible contestants shall include only (a) interns, residents, or graduate students in Obstetrics, Gynecology or Abdominal Surgery, and (b) physicians (with an M.D. degree) who are actively practicing or teaching Obstetrics, Gynecology or Abdominal Surgery.

(3) "Manuscripts must be presented under a nom-de-plume, which shall in no way indicate the author's identity, to the Secretary of the Association together with a sealed envelope bearing the nom-de-plume and containing a card showing the name and address of the contestant.

(4) "Manuscripts must be limited to 5,000 words, and must be typewritten in double-spacing on one side of the sheet. Ample margins should be provided. Illustrations should be limited to such as are required for a clear exposition of the thesis.

(5) "The successful thesis shall become the property of the Association, but this provision shall in no way interfere with the publication of the communication in the journal of the author's choice. Unsuccessful contributions will be returned promptly to their authors.

(6) "Three copies of all manuscripts and illustrations entered in a given year must be in the hands of the Secretary before June 1st.

(7) "The award will be made at the Annual Meetings of the Association, at which time the successful contestant must appear in person to present his contribution as a part of the regular scientific program, in conformity with the rules of the Association. The successful contestant must meet all expenses incident to this presentation.

(8) "The President of the Association shall annually appoint a Committee on Award, which, under its own regulations shall determine the successful contestant and shall inform the Secretary of his name and address at least two weeks before the annual meeting."

For further information, address Jas. R. Bloss, M.D., Secretary, 418 Eleventh Street, Huntington, W. Va.

ROSTER OF AMERICAN OBSTETRICAL AND GYNECOLOGICAL SOCIETIES*

(Appears in January, April, July, October)

American Gynecological Society. *President,* E. J. Litzenberg. *Secretary,* Richard W. TeLinde, 11 East Chase Street, Baltimore, Md. Next meeting, May 26 to 28, 1941, Broadmoor Hotel, Colorado Springs, Colo.

American Association of Obstetricians, Gynecologists and Abdominal Surgeons. *President,* Frederick H. Falls, Chicago, Ill. *Secretary,* James R. Bloss, 418 11th Street, Huntington, W. Va. Annual meeting will be held at the Homestead, Hot Springs, Va., September 11 to 13, 1941.

Central Association of Obstetricians and Gynecologists. *President,* Thomas B. Sellers, New Orleans, La. *Secretary-Treasurer,* W. F. Mengert, Iowa City, Iowa. Next meeting, New Orleans, La., Fall of 1941.

South Atlantic Association of Obstetricians and Gynecologists. *President,* R. A. Bartholomew, Atlanta, Ga. *Secretary,* Robert A. Ross, Durham, N. C. Next meeting, February, 1942, Atlanta, Ga.

A. M. A. Section on Obstetrics and Gynecology. *Chairman,* Norman F. Miller, Ann Arbor, Mich. *Secretary,* Philip F. Williams, 2206 Locust St., Philadelphia, Pa. Next meeting, June 2 to 6, 1941, Cleveland, Ohio.

New York Obstetrical Society. *President,* Thomas C. Peightal. *Secretary,* Ralph A. Hurd, 37 E. 64th Street, New York City. Second Tuesday, from October to May, Yale Club.

Obstetrical Society of Philadelphia. *President,* Roy W. Mohler. *Secretary,* John C. Hirst, 500 North 20th St., Philadelphia, Pa. First Thursday, from October to May.

Chicago Gynecological Society. *President,* Harold K. Gibson. *Secretary,* James A. Gough, 104 S. Michigan Ave., Chicago, Ill. Third Friday, from October to June, Hotel Knickerbocker.

Brooklyn Gynecological Society. *President,* George G. Cochran. *Secretary,* John J. Madden, 362 Washington, Ave., Brooklyn N. Y. First Friday, from October to May, Kings County Medical Society, 1313 Bedford Avenue, Brooklyn, N. Y.

Baltimore Obstetrical and Gynecological Society. *President,* Abraham Samuels, *Secretary-Treasurer,* Frank K. Morris, 11 East Chase St., Baltimore, Md. Meets quarterly at Maryland Chirurgical Faculty Building.

Cincinnati Obstetrical Society. *President,* E. W. Enz. *Secretary,* Edward Friedman, 19 West Seventh St., Cincinnati, O. Third Thursday of each month.

Louisville Obstetrical and Gynecological Society. *President,* Robert F. Monroe. *Secretary,* Layman A. Gray, 332 West Broadway, Louisville, Ky. Fourth Monday, from September to May, Brown Hotel.

Portland Society of Obstetrics and Gynecology. *President,* Howard Stearns. *Secretary,* William M. Wilson, 545 Medical Arts Bldg., Portland, Ore. Last Wednesday of each month.

Pittsburgh Obstetrical and Gynecological Society. *President,* S. A. Chalfant. *Secretary,* Joseph A. Hepp, 121 University Place, Pittsburgh, Pa. First Monday of October, December, February, April, and June.

Obstetrical Society of Boston. *President,* John Rock. *Secretary,* Judson A. Smith, 264 Beacon St., Boston, Mass. Third Tuesday, October to March, Harvard Club.

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*Changes, omissions, and corrections should be addressed to the Editor of the JOURNAL.

New England Obstetrical and Gynecological Society. *President,* Frederick L. Good. *Secretary,* R. J. Heffernan, 475 Commonwealth Avenue, Boston, Mass. Meetings held in May and December.

Pacific Coast Obstetrical and Gynecological Society. *President,* John Vruwink. *President-Elect,* T. Floyd Bell. *Secretary-Treasurer,* William Benbow Thompson, 6253 Hollywood Boulevard, Los Angeles, Calif. Next meeting, Los Angeles, Calif., November 5 to 8, 1941.

Washington Gynecological Society. *President,* R. L. Sylvester. *Secretary,* W. R. Thomas, 1830 K. Street, N. W., Washington, D. C. Fourth Saturday, October to May.

New Orleans Obstetrical and Gynecological Society. *President,* E. L. Zander. *Secretary,* Eugene Countiss, 921 Canal St., New Orleans, La. Meetings held every other month.

St. Louis Gynecological Society. *President,* E. Lee Dorsett. *Secretary,* Joseph A. Hardy, Jr., 4952 Maryland Ave., St. Louis, Mo. Second Thursday, October, December, February, and April.

San Francisco Gynecological Society. *President,* T. Henshaw Kelly. *Secretary,* R. Glenn Craig, 490 Post Street, San Francisco, Calif. Regular meetings held second Friday in month, University Club, San Francisco, or Claremont Country Club, Oakland, Calif.

Texas Association of Obstetricians and Gynecologists. *President,* Roy Grogan. *Secretary,* J. McIver, 714 Medical Arts Building, Dallas, Texas. Next meeting, Galveston, Texas, September, 1941.

Michigan Society of Obstetricians and Gynecologists (formerly the Detroit Obstetrical and Gynecological Society). *President,* Russell W. Allen. *Secretary,* Harold C. Mack, 955 Fischer Bldg., Detroit, Mich. Meeting first Tuesday of each month from October to May (inclusive).

Obstetric Society of Syracuse Hospitals. *President,* Francis R. Irving. *Secretary,* Nathan N. Cohen, 713 East Genesee St., Syracuse, N. Y. Meets second Tuesday of September, November, January, March, and May.

Alabama Association of Obstetricians and Gynecologists. *President,* T. M. Boulware, Birmingham, Ala. *Secretary,* Eva F. Dodge, 519 Dexter Avenue, Montgomery, Ala. Next meeting, Mobile, Ala., April, 1941.

San Antonio Obstetric Society. *President,* I. T. Cutter. *Secretary,* S. Foster Moore, Jr., San Antonio, Texas. Meetings held first Tuesday of each month at Gunter Hotel.

Books Received

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY. By Charles Mazer, M.D., F.A.C.S., Assistant Professor of Gynecology and Obstetrics, Graduate School of Medicine, University of Pennsylvania, etc., and S. Leon Israel, M.D., F.A.C.S., Instructor in Gynecology and Obstetrics, School of Medicine, University of Pennsylvania. With 108 illustrations, 485 pages. Paul B. Hoeber, Inc., New York City, 1941.

PHARMACOLOGICAL BASIS OF THERAPEUTICS. By Louis Goodman, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University, School of Medicine, and Alfred Gilman, Ph.D., Assistant Professor of Pharmacology and Toxicology, Yale University, School of Medicine. 126 figures, 1383 pages. The Macmillan Company, New York, 1941.

TECHNIQUES OF CONTRACEPTION CONTROL. By Robert Latou Dickinson, M.D., and Woodbridge Edwards Morris, M.D., General Medical Director, Birth Control Federation of America. 50 illustrations, 56 pages. The Williams & Wilkins Company, Baltimore, 1941.

WILLIAMS OBSTETRICS. By Henricus J. Stander, M.D., F.A.C.S., Professor of Obstetrics and Gynecology, Cornell University Medical College, etc. Eighth edition, 704 illustrations, 1401 pages. D. Appleton-Century Company, Inc., New York, 1941.